Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

New Strategies for the Functionalization of *N*-Heterocycles using Li-, Mg- and Zn-Organometallics

von

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aus

München, Deutschland

2014

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Professor Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

München, 22. Mai 2014

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Nadja Maria Barl

Dissertation eingereicht am: 26. Mai 2014

1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Konstantin Karaghiosoff

Mündliche Prüfung am: 26. Juni 2014

This work was carried out from May 2011 to May 2014 under the guidance of Prof. Dr. Paul Knochel at the Department of Chemistry at the Ludwig-Maximilians-Universität Munich.

First, I would like to express my appreciation to Prof. Dr. Paul Knochel for giving me the great opportunity to carry out my PhD thesis in his group, for his guidance and support in the course of my scientific research and for the wonderful pipe he gave me as a present.

I am also very grateful to Prof. Dr. Konstantin Karaghiosoff for agreeing to be second reviewer of this thesis and I thank all members of my defense committee – Prof. Dr. Manfred Heuschmann, Prof. Dr. Heinz Langhals, Prof. Dr. Hans-Christian Böttcher and Dr. Thomas Magauer – for their interest shown in this manuscript by accepting to be referees.

Veronika Werner, Sophia Manolikakes, Julia Nafe and Thomas Klatt, who have been diligently proofreading this manuscript, have been of invaluable help, thank you!

I want to extend my gratitude in particular to Dr. Andreas "Wagolette" Wagner, Dr. Milica "Milka" Jaric, Veronika "Vroni" Werner, Olesya "Чувиха" Kuzmina and Christoph "Schneemann" Sämann. Vroni, thank you for being my rock during the past three years! And even though we did not get along so well in the beginning, I would not want to miss you as a good friend anymore! Wagner, I'm so grateful to you for teaching me Russian and Arabic and the nice coffee breaks we had during our studies! To me, that was probably the best recover from chemistry I could imagine. Milka, for you my "Bifi" is always open. Чувиха, желаю тебе всего самого лучшего для тебя и твоего поросёночка. Schneemann, thank you for being one of the guys to stay with me until the very end of every party!

I greatly thank my labmates in F2.001b, without you it would have not been the same: Sophia "Sophula" "Knuffel" Manolikakes, Julia "Oberasi" Nafe, Matthias "Matze" Becker and Andreas "Tank" "Steiff" Steib. Sophula, I also thank you for always lending me an ear and for the nice Rhodos-trip we had! Julia, it was nice to have somebody to stay with me until 10 pm, to curse as loud as me and to share the "Palle-Partybus" on the way home! To all my bench neighbors Dr. Tobias "Blümchen" Blümke, Mario Ellwart and Andreas "Steiff" Steib, thank you for the the nice atmosphere. Blümchen, thank you for helping me in the beginning and for entertaining me with your explosive emotions. Steiff, you were the best bench neighbour I had! Our "deep" discussions, sometimes involving our good friends Toni and Jamy, really extended my horizon.

I would like to thank Annette Frischmuth, Dr. Maitane Fernández and especially Dr. Elodie Sansiaume-Dagousset for the successful collaborations. Elodie, I still miss you a lot! I will not forget "La Passion de Nadja et Elodie" and the laughs we had together.

Renate Schröder, Vladi "Waldimir" Malakhov and Yulia Tsvik have been most helpful in organizing everyday life in the lab and the office. Thank you!

I thank my mother, my stepfather and my Allgäu-Opa for both financial and mental support and for all they have done for me! Last, but definitely not least, I want to express my deep appreciation and love for Daniel "Schlingel" Hofmeister. Thank you, for holding my back, for always supporting me, for making me laugh even though I wanted to cry and for existing! I could not imagine my life without you anymore!

Parts of this PhD thesis have been published

Communications

1. N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff, P. Knochel: "Full-Functionalization of the 7-Azaindole Scaffold *via* Selective Metalation and Sulfoxide/Magnesium-Exchange", *Angew. Chem. Int. Ed.* **2013**, *52*, 10093. (Highlighted in: *Synfacts* **2013**, 1272)
2. N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel: "Preparation and Reactions of Heteroarylmethylzinc Reagents", *Org. Lett.* **2014**, *16*, 2422.
3. A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel: "New *in situ* Metalations of Functionalized Arenes and Heterocycles with TMPLi in the Presence of $ZnCl_2$ and other Metal Salts", *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/anie.201403688.
4. N. M. Barl, V. Malakhov, C. Mathes, P. Knochel: "Pd-Catalyzed Cross-Coupling between 7-Azaindoles and *Reformatsky* Reagents", *manuscript in preparation*.

Reviews

1. S. M. Manolikakes, N. M. Barl, C. Sämann, P. Knochel, "Regioselective Functionalization of Pyridines Using a Directed Metalation or a Halogen/Metal Exchange", *Z. Naturforsch.* **2013**, *68b*, 411.
2. N. M. Barl, V. Werner, C. Sämann, P. Knochel, "The Halogen/Magnesium Exchange Using *i*PrMgCl·LiCl and Related Exchange Reagents", *Heterocycles* **2014**, *88*, 827.

Für Schlingel und

Meine Familie

“Wir denken selten an das, was wir haben, aber immer an das, was uns fehlt.“

- Arthur Schopenhauer -

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A. INTRODUCTION

1. OVERVIEW

"*Nowadays, it is not only unwise but rather difficult to accomplish an efficient and selective multiple synthesis without using organometallics.*"[1]

Already 30 years ago, the 2010 Nobel-Prize laureate *Ei-ichi Negishi* announced the essential role organometallic chemistry should later play in modern organic synthesis. Especially nowadays, having the world's population from now on growing by 33% until 2050,[2] mankind is confronted with new technological challenges. Limited resources such as water, fossil materials and energy, the consequently increasing prices for raw materials, as well as the climate change caused by human interference put a lot of pressure on modern technologies,[3] making the finding of new concepts for the supply of basic chemicals and a change towards more sustainable chemistry indispensable.[4] Particularly, the pharmaceutical sector is known for producing a major amount of waste accumulated in chemical industries. For example, the total synthesis of natural products and the preparation of therapeutical agents often involve tedious protective group manipulations and long, yield-reducing linear reaction sequences[5] leading to poor atom-economy.[6] As organic chemistry is key for the production of small molecules as well as more sophisticated and complex materials such as polymers, pharmaceutics and natural products, the fundamental task of modern organic synthesis must be a combination of minimal waste production due to atom-economical strategies,[7] synthetic efficiency and a low E-factor.[8]

In this context, organometallic chemistry fulfils many of these requirements and has given way to a wide range of synthetic transformations which were not accessible using conventional strategies. Due to the unique reactivity and selectivity depending on the nature of the metal used, a plethora of organometallic compounds is available, which has found numerous applications in organic synthesis as reagents as well as catalysts.[9] The

[1] E.-i. Negishi, *Organometallics in Organic Synthesis*, Wiley-VCH, Weinheim, **1980**.
[2] Population Division of the Department of Economic and Social Affairs oft he United Nations Secretariat, World Population Prospects. The 2010 Revision. Worls Population change per year (thousands) Medium variant 1950-2050.
[3] R. H. Crabtree, *Organometallics* **2011**, *30*, 17.
[4] a) T. Collins, *Science* **2001**, *291*, 48. b) C. Okkerse, H. van Bekkum, *Green Chemistry* **1999**, *1*, 107.
[5] *Organic Synthesis* (Eds.: J.-H. Fuhrhop, G. Li) Wiley-VCH, Weinheim, **2003**.
[6] a) *Protective Groups in Organic Synthesis 3rd Ed.*, (Eds.: T.W. Green, P. G. Wuts) Wiley & Sons, Hoboken, **1999**. b) *Protecting Groups 3rd Ed.* (Ed.: P. J. Kocienski) Thieme, New York, **2005**.
[7] a) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259. b) B. M. Trost, *Science* **1991**, *254*, 1471.
[8] a) R. A. Sheldon, *Chem. Ind.* (London), **1992**, 903. b) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273. c) R. A: Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.
[9] a) *Handbook of Functionalized Oganometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**. b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**. c) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

properties of organometallic reagents are strongly dependent on the polarity of the carbon-metal bond which is determined by the differences in electronegativity. An increased ionic character, as it is found in organolithium and organosodium compounds, indeed leads to an increased reactivity. However, even at low temperatures, the tolerance towards sensitive groups and the selectivity decrease in these reagents.[10] Organometallics such as organoboron reagents show a rather covalent character in the carbon-metal bond resulting in an improved tolerance towards sensitive functional groups. In contrast to this, these compounds are characterized by a lack of reactivity enforcing harsh reaction conditions or highly developed catalytic systems to ensure proper reactions with electrophiles.[11] In this context, organomagnesium, -copper and -zinc reagents display a valuable compromise between reactivity and selectivity. Organomagnesium compounds have been reported to be highly reactive, but indeed compatible with a wide range of senstitive moieties when employed at low temperature.[12] In addition, copper reagents readily undergo reactions with a number of electrophiles and show a good functional group tolerance.[13] However, their thermal instability and their preparation by transmetalation of other organometallic reagents such as Li- and Mg-compounds display major disadvantages.[14] On the other hand, due to their low reactivity, organozinc reagents show an exceptional functional group tolerance[15] and are characterized by a great thermal stability.[12] Their reactivity problems can be readily overcome by transmetalation reactions with suitable transition metal catalysts such as Co, Cu, Ni and Pd.[16] Especially with the non-polar organozinc compounds, transmetalation is alleviated by empty low-lying *p*-orbitals enabling a smooth interaction with the *d*-orbitals of transition metals.[9a,15a]

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[10] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[11] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[12] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[13] a) P. Knochel, M. J. Rozema, C. E. Tucker, *Preparation of Highly Functionalized Copper Reagents* in *Practical Approach Series in Chemistry - Organocopper Reagents*, (Ed.: R. J. K. Taylor), Oxford University Press, **1993**, 348. b) *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**.
[14] a) *Organometallics in Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **1980**. b) For halogen-copper exchange reactions, see: i) X. Yang, T. Rotter, C. Piazza, P. Knochel, *Org. Lett.* **2003**, *8*, 1229. ii) X. Yang, P. Knochel, *Synlett* **2004**, *1*, 81. iii) M. I. Calaza, X. Yang, D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *8*, 1229. iv) X. Yang, A. Althammer, P. Knochel, *Org. Lett.* **2004**, *6*, 1665. c) For direct insertion of highly reactive copper, see: i) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1984**, *49*, 5280. ii) R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 5056. iii) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1988**, *53*, 4482.
[15] a) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417. b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**.
[16] a) *Metal-Catalyzed Cross-Coupling Reactions 2nd Ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**. b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley-VCH, New York, **2002**. c) *Transition Metals for Organic Synthesis 2nd Ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2002**.

Thus, even rather unreactive organozinc compounds are able to undergo various reactions with less electrophilic molecules.

2. ORGANOMAGNESIUM REAGENTS

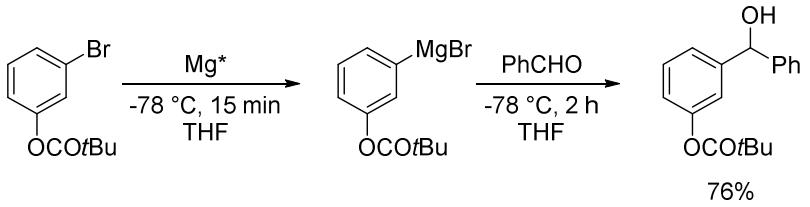
2.1 OXIDATIVE ADDITION OF MAGNESIUM TO CARBON-HALOGEN BONDS

When *Philippe Barbier*'s student *Victor Grignard* discovered the organomagnesium compounds in 1900,[17] he probably never dreamed of these reagents soon to become "*…the most important of all organometallic compounds encountered in the chemical laboratory*".[18] By direct magnesium insertion into the carbon-iodide bond of methyliodide, *Grignard* managed to establish the first, straightforward approach for the preparation of these organometallic compounds in etheral solutions.[17] Despite of extensive studies performed by chemists and physicists, the exact mechanism of the insertion reaction is still not entirely clarified, but a radical pathway is generally accepted.[19] However, since then, these *Grignard* reagents have found numerous applications in chemical laboratories and in chemical industry.[20]

Yet, the method of the direct magnesium insertion generally shows several drawbacks. On the one hand, the efficiency of the insertion reaction itself is hampered by the low atom-economy.[7] On the other hand, due to the highly exothermic initiation step using activating agents such as dibromoethane or iodine for the generation of an active metal surface, their preparation in plant scale bears serious safety risks.[21] This fact also leads to a limited functional group tolerance extremely impeding the scope of this reaction.

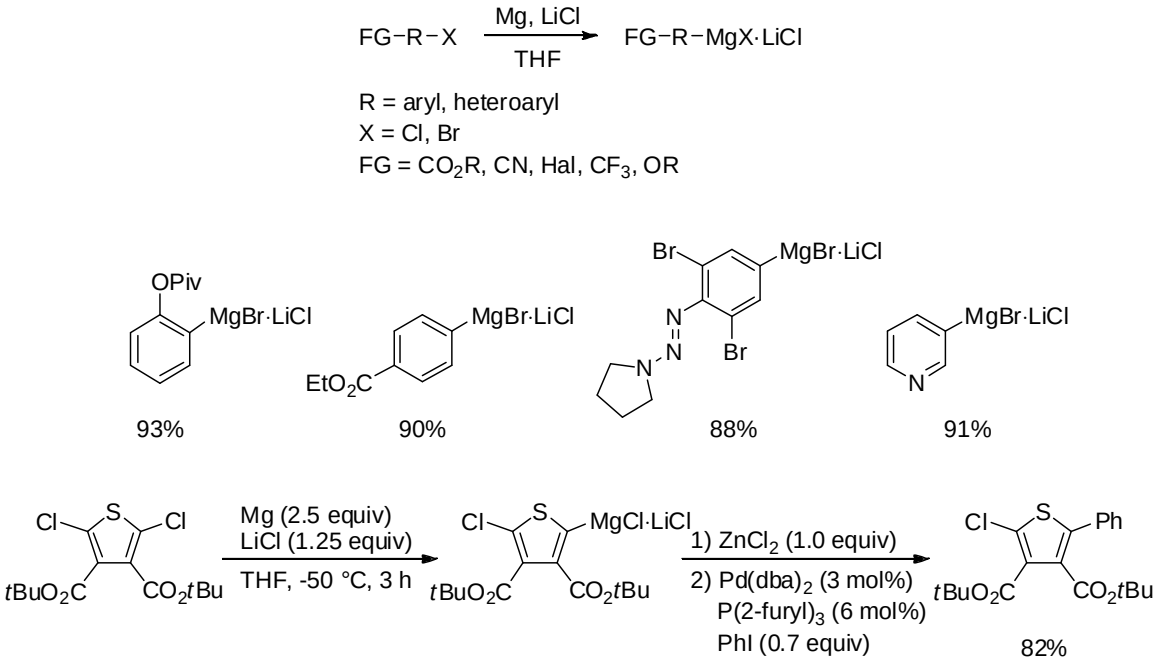
In 1972, *Rieke* and co-workers reported a new method for the preparation of *Grignard* reagents which successfully overcomes these flaws. By reduction of anhydrous magnesium salts using the alkali metal lithium and naphthalene as electron carrier, highly reactive and pyrophoric magnesium (Mg*) was obtained allowing the generation of organomagnesium reagents at very low temperatures and hence, making this strategy compatible with sensitive functional groups such as esters and nitriles (Scheme 1).[22]

[17] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[18] *The Main Group Elements* (Eds.: G. E. Coates, K. Wade), Methuen, London, **1967**.
[19] a) H. M. Walborksy, *Acc. Chem. Res.* **1990**, *23*, 286. b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95. c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[20] a) *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **2000**. b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey Jr.), Wiley-VCH, New York, **2000**. c) J. Wiss, M. Länzlinger, M. Wermuth, *Org. Proc. Res. Dev.* **2005**, *9*, 365.
[21] M. C. Jones, *Plant and Operations Progress* **1989**, *8*, 200.
[22] a) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178. b) R. D. Rieke, *Science* **1989**, *246*, 1260. c) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. d) J. Lee, R. Verlade-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428. e) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.



Scheme 1: Preparation and reactivity of a functionalized *Grignard* reagent using highly reactive *Rieke*-Mg (Mg*).

Nevertheless, the tedious activation of the magnesium prior to its use and the need for very low reaction temperatures makes the *Rieke* method quite disadvantageous at times. Thus, *Knochel* and co-workers established a new strategy for the preparation of organomagnesium reagents by the direct magnesium insertion into organic halides in the presence of stoichiometric amounts of LiCl.[23] Under mild reaction conditions, this methodology gives rise to a wide range of new (hetero)aryl magnesium compounds accessible from the corresponding bromides and even chlorides (Scheme 2).



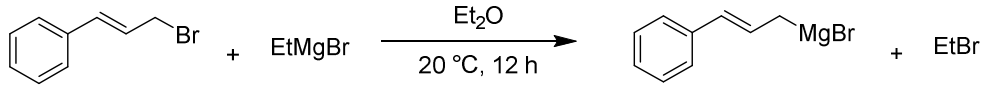
Scheme 2: Preparation of functionalized (hetero)aryl magnesium reagents using Mg in the presence of LiCl.

2.2 HALOGEN/MAGNESIUM EXCHANGE

A wide range of viable organomagnesium reagents is also accessible *via* halogen/magnesium exchange reactions. In contrast to insertion reactions, the homogeneity of the halogen/magnesium exchange bears certain advantages. Since these

[23] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

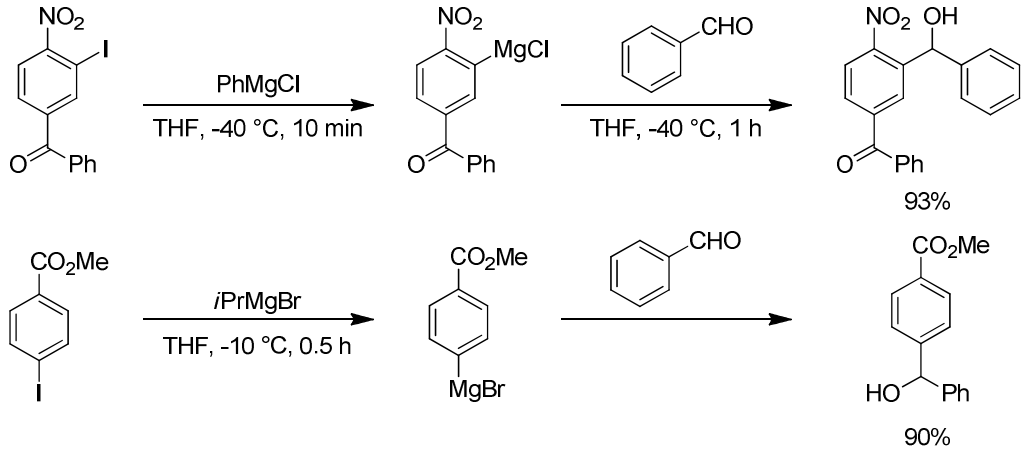
reactions are performed under very mild conditions, the functional group tolerance is clearly improved. The first halogen/magnesium exchange was reported by *Prevóst* in 1931 by reaction of cinnamyl bromide with ethylmagnesium bromide (Scheme 3).[24]



Scheme 3: First example of a halogen/magnesium exchange reported by Prevóst.

This method has found numerous applications and gave access to organometallic reagents such as magnesium carbenoids which, so far, were difficult to prepare by direct magnesium insertion.[25,26] The halogen/magnesium exchange is considered as an equilibrium in which the driving force of the exchange reaction is the formation of the most stable organomagnesium species. In that manner, compared to the exchange reagent itself, the thus-prepared organometallic compound posseses a higher thermodynamic stability ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[27]

In 1998, the methodology of the halogen/magnesium exchange could be further extended by *Knochel* and co-workers describing the iodine/magnesium exchange with PhMgCl and *i*PrMgBr at low temperatures and thus, enabling the use of substrates bearing sensitive functionalities (Scheme 4).[28]

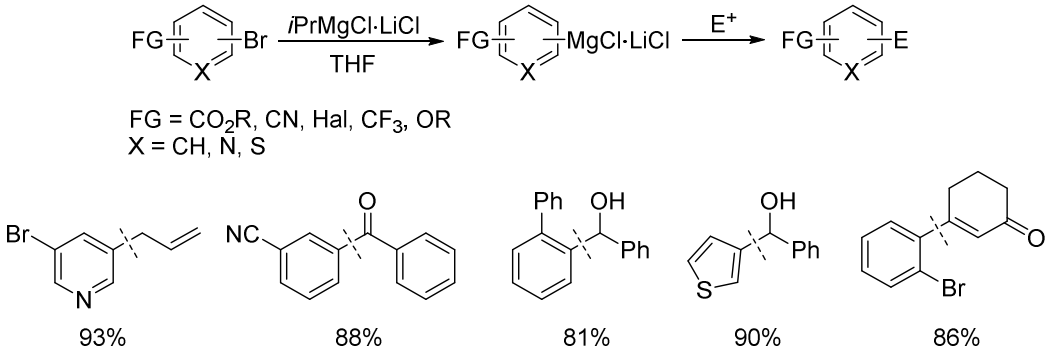


Scheme 4: Preparation and reactivity of functionalized *Grignard* reagents by iodine/magnesium exchange using PhMgCl or *i*PrMgBr.

[24] C. Prevóst, *Bull. Soc. Chim. Fr.* **1931**, 1372.
[25] a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, 1520. b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470.
[26] a) C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153. b) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1987**, *28*, 5845. c) D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189. d) G. Cahiez, D. Bernard, J. F. Normant, *J. Organomet. Chem.* **1976**, *113*, 107. e) C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.
[27] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev*. **2006**, *10*, 733.
[28] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701. b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610. c) I. Sapountzis, H. Dube, R. Lewis, N. Gommermann, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2445.

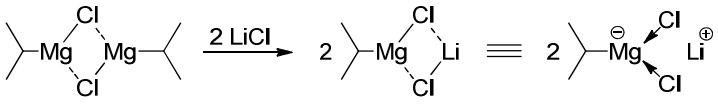
While the exchange reaction on (hetero)aryl iodides proceeds smoothly with these exchange reagents even on moderately activated substrates, aryl and heteroaryl bromides are much more reluctant to undergo a Br/Mg exchange. Either a directing group[29] has to be present in the organic bromide, which readily chelates the exchange reagent,[30] or rather harsh conditions such as elevated temperatures[31] are required for a successful exchange reaction.

To overcome these problems, *Knochel* and co-workers recently developed the so-called "Turbo-*Grignard*" *i*PrMgCl·LiCl showing a remarkably higher reactivity and hence, broadening the scope of the exchange reaction to such extend that even rather unactivated (hetero)aryl bromides are successfully converted into the corresponding magnesium reagents (Scheme 5).[27,32]



Scheme 5: Preparation and reactivity of functionalized *Grignard* reagents by bromine/magnesium exchange using the Turbo-*Grignard* reagent (*i*PrMgCl·LiCl).

The reactivity-boost of the Turbo-*Grignard* is attributed to the complexation of LiCl leading to a magnesium-lithium ate-species which significantly increases the solubility and the nucleophilicity of both the exchange reagent and the resulting *Gignard* reagent due to deaggregation of the magnesium species (Scheme 6).[32]



Scheme 6: Effect of LiCl on *Grignard* reagents.

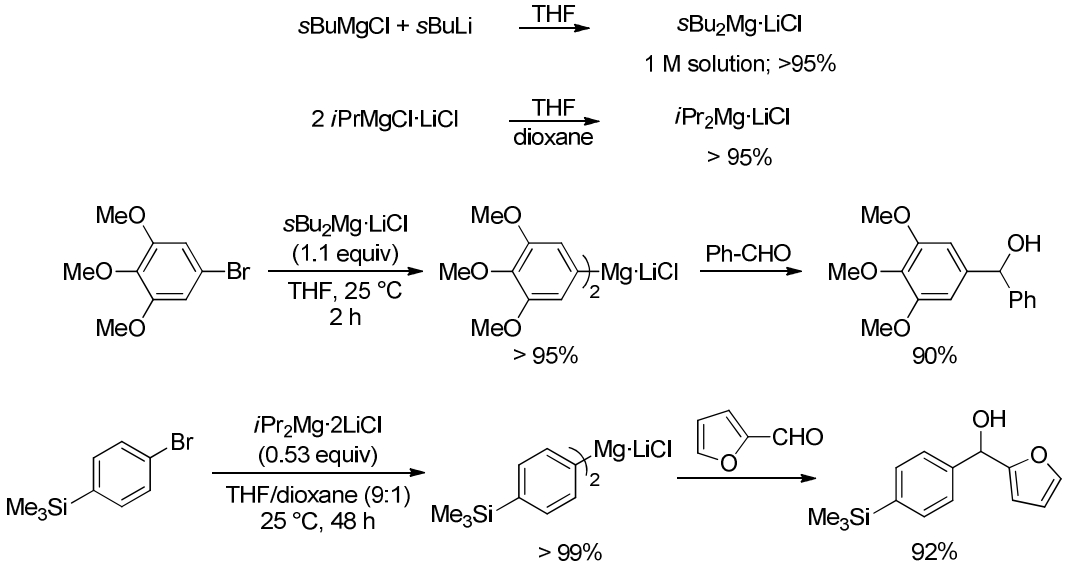
[29] a) M. O. Kitching, V. Snieckus, *Nature* **2012**, *486*, 478. b) M.C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879. d) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306.

[30] a) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449. b) M. Abarbri, F. Dehmel, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.

[31] H. Nishiyama, K. Isaka, Kenji Itoh, K. Ohno, H. Nagase, K. Matsumoto, H. Yoshiwara, *J. Org. Chem.* **1992**, *57*, 407.

[32] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. c) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726. d) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543. e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

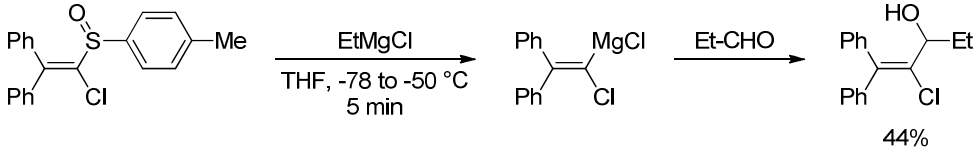
The halogen/magnesium exchange works well for electron-deficient systems. However, in cases where the electron-density of the arene is rather high, *i*PrMgCl·LiCl fails to readily convert these compounds to the corresponding magnesium species. To this end, *bis*-magnesium reagents of type $RMg_2 \cdot LiCl$ have been established, showing, according to quantum-chemical calculations, that the exchange reaction is more likely to proceed when the ate-character of the exchange reagent is enhanced.[32b] In this context, the *Grignard* reagents *s*$Bu_2Mg \cdot LiCl$ and *i*$Pr_2Mg \cdot LiCl$ were developed and could successfully be employed in exchange reactions with comparably unreactive aryl bromides and iodides (Scheme 7).[32b]



Scheme 7: Use of $R_2Mg \cdot LiCl$ as exchange reagents for electron-rich aromatics.

2.3 SULFOXIDE/MAGNESIUM EXCHANGE

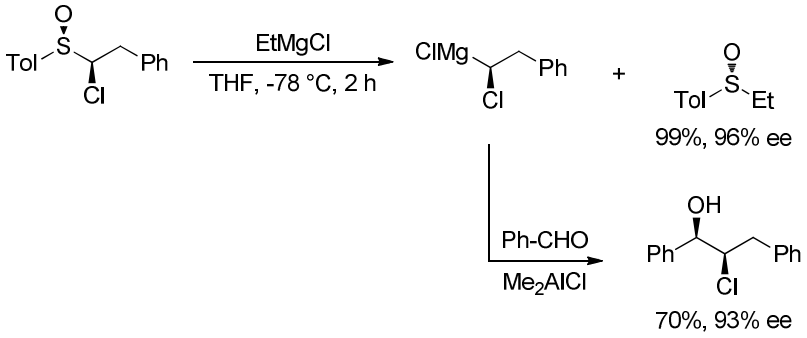
Not only halogenated substrates display suitable precursors for the performance of a magnesium exchange. In 1995, *Satoh* and co-workers presented their pioneering work on several sulfoxide/magnesium exchanges employing α-chloro-substituted vinyl sulfoxides, which were readily converted into the corresponding *Grignard* reagents upon treatment with ethylmagnesium chloride (Scheme 8).[33]



Scheme 8: Sulfoxide/magnesium exchange on α-chloro-substituted vinyl sulfoxides.

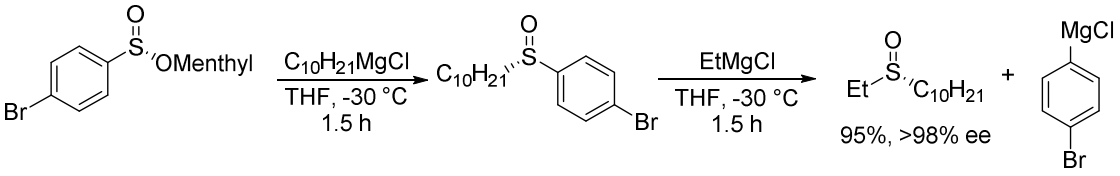
[33] a) T. Satoh, K. Takano, H. Someya, K. Matsuda, *Tetrahedron Lett.* **1995**, *36*, 7097. b) For leading references see: T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557. c) For a review, see: T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.

Further extensions could be accomplished by *Satoh*[34] and *Hoffmann*[35] who reported the preparation of chiral magnesium reagents which reacted with electrophiles to produce substrates bearing a second chiral center transferring the enantiomeric purity (Scheme 9). Noteworthy, this reaction proceeds under inversion of the configuration at the sulphur atom.



Scheme 9: Sulfoxide/magnesium exchange on chiral α-chloro-substituted alkyl sulfoxides.

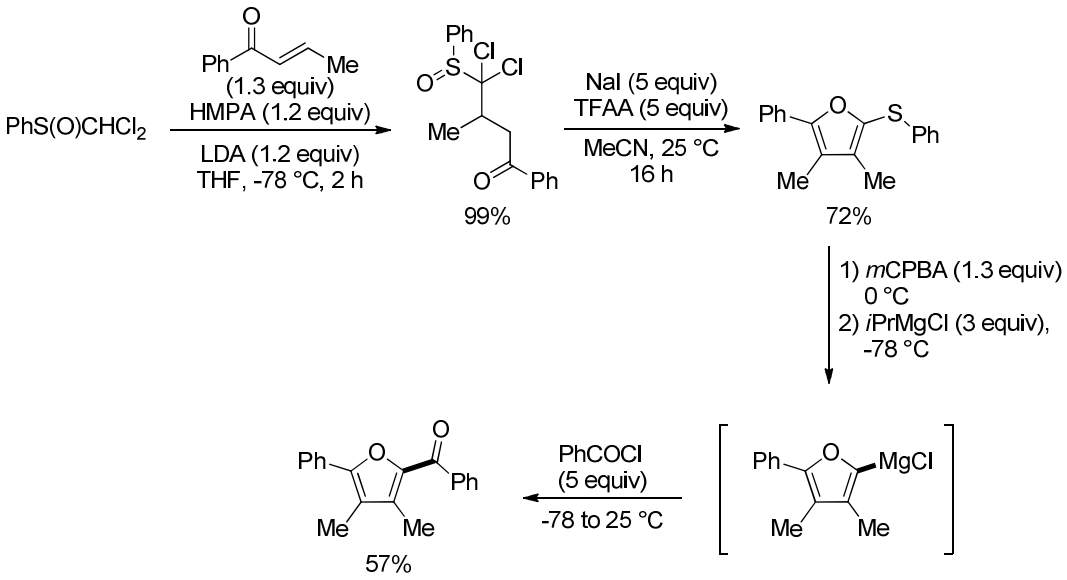
Lockhard, *Capozzi* and *Naso* exploited the sulfoxide/magnesium exchange for the enantioselective synthesis of dialkyl sulfoxides starting from chiral sulfinyl derivatives which had been prepared by the *Andersen*[36] sulfinate (Scheme 10).[37]



Scheme 10: Preparation of chiral dialkyl sulfoxides.

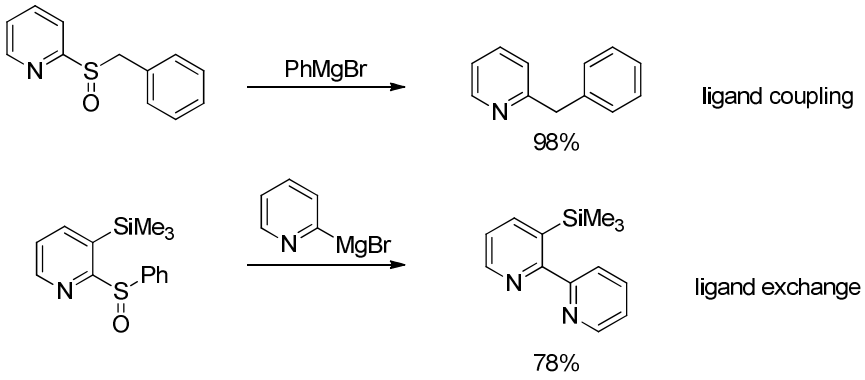
However, most of the reported studies mainly focused on the synthesis of chiral substrates starting from the chiral sulfoxides, without paying much attention to the formation of valuable *Grignard* reagents during the exchange reactions. In 2007, *Satoh* described the synthesis of functionalized furans and reported therein the preparative utilization of sulfinyl groups (Scheme 11).[38] Yet, the methodology only shows little functional group compatibility and suffers from the necessity to use excess of reagents.

[34] a) T. Satoh, D. Taguchi, C. Suzuki, S. Fujisawa, *Tetrahedron* **2001**, *57*, 493. b) T. Satoh, K. Akita, *Chem. Pharm. Bull.* **2003**, *51*, 181. c) T. Satoh, M. Miura, K. Sakai, Y. Yokoyama, *Tetrahedron* **2006**, *62*, 4253. d) S. Sugiyama, H. Shimizu, T. Satoh, *Tetrahedron Lett.* **2006**, *47*, 8771.
[35] a) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 3072. b) B. Hölzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732. c) R. W. Hoffmann *Chem. Soc. Rev.* **2003**, *32*, 225.
[36] a) K. K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93. b) K. K. Andersen, W. Gaffield, N. E. Papanikolau, J. W. Foley, R. I. Perkins, *J. Am. Chem. Soc.* **1964**, *86*, 5637.
[37] a) J. P. Lockard, C. W. Schroeck, C. R. Johnson, *Synthesis* **1973**, 485. b) M. A. M. Capozzi, C. Cardellicchio, F. Naso, V. Rosito, *J. Org. Chem.* **2002**, *67*, 7289. c) For a review, see: M. A. M. Capozzi, C. Cardellicchio, F. Naso, *Eur. J. Org. Chem.* **2004**, *9*, 1845.
[38] T. Miyagawa, T. Satoh, *Tetrahedron Lett.* **2007**, *48*, 4849.



Scheme 11: Synthesis of a tetrasubstituted furane using the sulfinyl group.

The groups of *Oae* and *Furakawa* further exploited the sulfoxide/magnesium exchange and discovered that exchanges performed on heteroaryl sulfoxides using different organometallic reagents led either to ligand exchange or ligand coupling reactions (Scheme 12).[39]



Scheme 12: Ligand coupling and ligand exchange reactions on 2-pyridyl sulfoxides.

Recently, *Knochel* and co-workers successfully applied this sulfoxide/magnesium exchange to the regioselective functionalization of various aromatics and heteroaromatics.[40]

[39] a) S. Oae, T. Kawai, N. Furukawa, *Tetrahedron Lett.* **1984**, *25*, 69. b) T. Kawai, N. Furukawa, *Tetrahedron Lett.* **1984**, *25*, 2549. c) S. Oae, *Phosphorus and Sulfur* **1986**, *27*, 13. d) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1989**, *30*, 7091. e) T. Shibutani, H. Fujihara, N. Furukawa, *Tetrahedron Lett.* **1991**, *32*, 2943.

[40] a) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362. b) F. Kopp, G. Sklute, K. Polborn, I. Marek, P. Knochel, *Org. Lett.* **2005**, *7*, 3789. c) C. B. Rauhut, L. Melzig, P. Knochel, *Org. Lett.* **2008**, *10*, 3891. d) L. Melzig, C. B. Rauhut, P. Knochel, *Synthesis* **2009**, 1041. e) L. Melzig, C. B. Rauhut, P. Knochel, *Chem. Commun.* **2009**, 3536.

2.4 DIRECTED METALATION WITH AMIDE BASES

Besides the interconversions mentioned above, organomagnesium compounds are as well accessible *via* a direct metalation using magnesium amide bases.[41] Main advantage of this method is the lack of an obligatory carbon-halogen bond present in the substrate, since such organic halides are usually quite "expensive" and have to be prepared prior to use. The directed deprotonative metalation, in contrast, readily employs a more or less activated hydrogen-carbon bond for the transformation into the corresponding magnesium species.

Up to now, a wide range of Mg-amide bases has been developed. Based on the pioneering work of *Meunier*,[41a] further extensions in this field were achieved by *Hauser* developing the mild magnesium bases diethyl- and di*iso*propylaminomagnesium bromide, which later on should be called the "*Hauser* bases".[41b,c] *Eaton*[42] and *Mulzer*[43] finally employed the more sterically hindered 2,2,6,6-tetramethylpiperidine (TMPH) as amine for their bases TMPMgCl, TMPMgBr and TMP_2Mg (TMP = 2,2,6,6-tetramethylpiperidyl). Yet, similarly to classic *Grignard* reagents, the organomagnesium reagents resulting from deprotonative metalation with these amide bases also show the tendency to form aggregates leading to a low solubility and a reduced reactivity. Consequently, for coping with these problems, a large excess of these bases and of the electrophiles had to be used. To this end, by developing the magnesium amides TMPMgCl·LiCl[44] and $TMP_2Mg \cdot 2LiCl$[45] (Turbo-*Hauser* bases), *Knochel* and co-workers have made an enormous improvement in this area.[46] Analogous to the exchange reagent *i*PrMgCl·LiCl, the stochiometric amount of LiCl leads to deaggregation and therefore, results in highly reactive mixed Mg/Li-amides which posess an excellent solubility in solvents such as THF. With these bases in hand, various functionalized aryl, heteroaryl and vinyl organomagnesium reagents could be prepared (Scheme 13).[44,46]

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[41] a) L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758. b) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. c) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350. d) A. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.

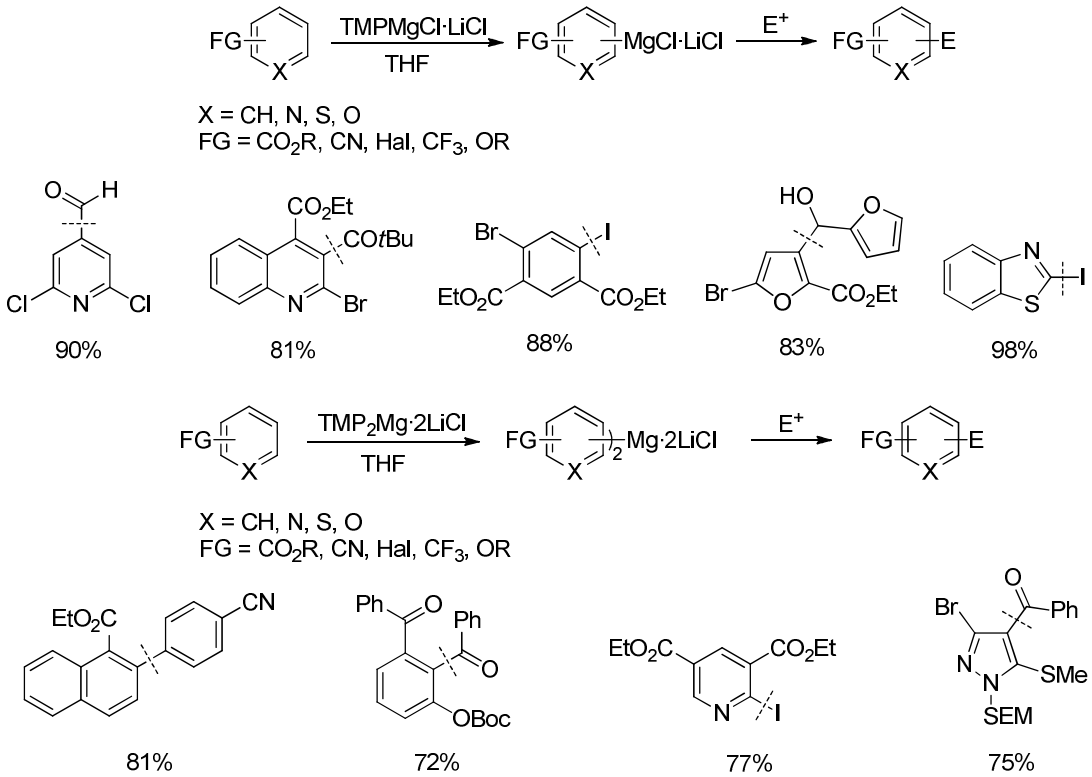
[42] P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.

[43] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.

[44] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. b) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525. c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497. d) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113.

[45] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. b) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374. c) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.

[46] For a recent review article about metalation reactions using hindered amide bases, see: B. A. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.



Scheme 13: Direct magnesiation using the Turbo-*Hauser* bases TMPMgCl·LiCl and $TMP_2Mg \cdot 2LiCl$, and subsequent reactions with electrophiles.

3. ORGANOZINC REAGENTS

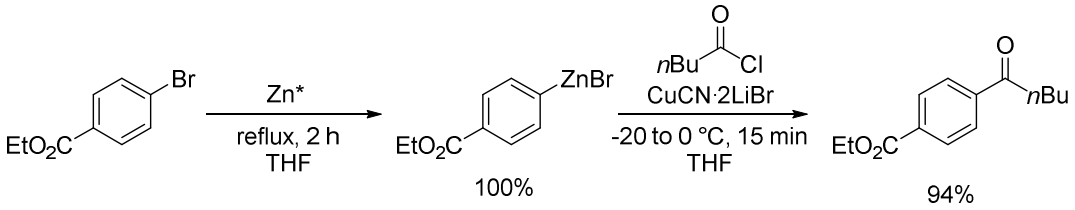
3.1 OXIDATIVE ADDITION OF ZINC TO CARBON-HALOGEN BONDS

The oxidative addition of zerovalent, elemental metal to a carbon-halogen bond was first discovered by *Robert Bunsen*'s student *Edward Frankland* in 1848.[47] With the synthesis of the pyrophoric diethylzinc by reaction of zinc with ethyliodide under inert hydrogen atmosphere,[47] *Frankland* synthesized the first organozinc reagent and paved the way for one of the most important methods applied up to now for the preparation of organometallics. However, due to their low reactivity, the actual potential of these organozinc reagents was not acknowledged during the first 80 years,[48] and thus, they only found few applications in organic synthesis including the *Reformatsky* reaction of zinc enolates[49] and the *Simmons-Smith* cyclopropanation reaction.[50] Furthermore, the easy access to organomagnesium[17,51] and organolithium reagents did not have a positive impact on the popularity of organozinc reagents either. Yet, their low reactivity is attributed to the rather covalent character of the carbon-zinc bond and leads to a high functional group tolerance, which, in contrast to organomagnesium and -lithium reagents, is even guaranteed at elevated temperatures.[9a,14,52] *Hunsdiecker* recognized the value of the properties accompanied by organozinc reagents and was responsible for their resurrection when he reported on the preparation of ester-substituted alkyl zinc iodides from zinc and the corresponding alkyl iodides in 1936.[53]

Thus, the direct insertion of zinc metal into organic halides constitutes one of the main approaches to organozinc reagents.[14] Though a broad range of sensitive functionalities such as esters, ketones and nitriles are well-tolerated, this method usually suffers from the necessity to use "expensive" organic iodides and elevated temperatures in polar solvents like HMPA, DMF, DMA or DMSO.[54] Some of these flaws could be overcome by *Rieke et al.* with the development of highly active zinc (Zn*), which, similarly to

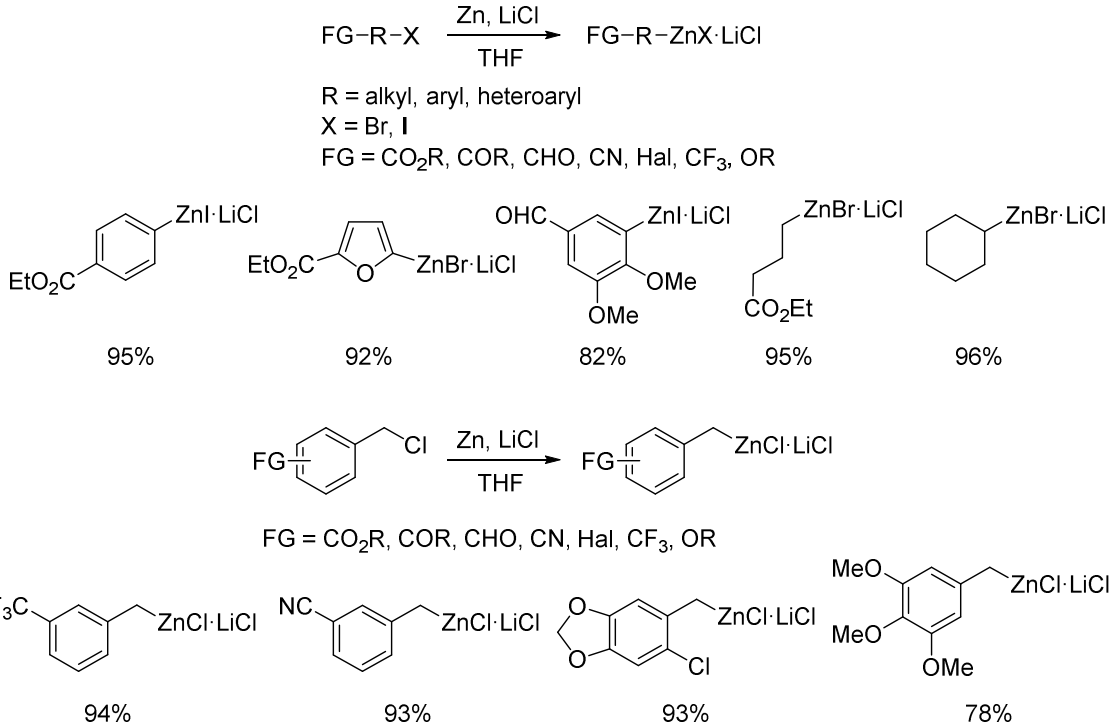
[47] a) E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171. b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[48] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[49] a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210, b) S. Reformatsky, *Chem. Ber.* **1895**, *28*, 2842. c) R. Ocampo, *Tetrahedron* **2004**, *60*, 9325. d) A. Fürstner, *Angew. Chem. Int. Ed.* **1993**, *32*, 164.
[50] a) H. E. Simmons, T. L. Cairns, A. Vladiuchick, C. M. Hoiness, *Org. React.* **1972**, *20*, 1. b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323. c) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 5323. d) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.
[51] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[52] a) P. Knochel, F. Langer, M. Rottländer, T. Stüdemann, *Chem. Ber.* **1997**, *130*, 387. b) P. Knochel, J. J. Almena Perea, P. Jones, P. *Tetrahedron* **1998**, *54*, 8275.
[53] H. Hunsdiecker, H. Erlbach, E. Vogt, *German Patent 722467*, **1942**.
[54] a) K. Tagaki, N. Hayama, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691. b) K. Tagaki, *Chem. Lett.* **1994**, 469. c) K. Tagaki, Y. Shimoishi, K. Sasaki, *Chem. Lett.* **1994**, 2055. d) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.

Mg*, is prepared by reduction of $ZnCl_2$ with lithium naphthalide, and gives access to a wide range of functionalized organozinc reagents starting from moderately activated organic bromides (Scheme 14).[22b-d,55]



Scheme 14: Preparation and reactivity of a functionalized organozinc reagent using highly reactive *Rieke*-Zn (Zn*).

Further improvements for the preparation of organozinc reagents by oxidative addition could be accomplished by *Knochel* and co-workers in 2006, establishing the LiCl-promoted insertion of zinc metal into organic halides.[56] Similarly to the effect of LiCl reported for the magnesium insertion,[23] the stoichiometric amount of this lithium salt results in a reactivity-boost enabling, besides aromatic and heteroaromatic bromides and iodides, also the use of alkyl bromides and benzyl chlorides in insertion reactions (Scheme 15).



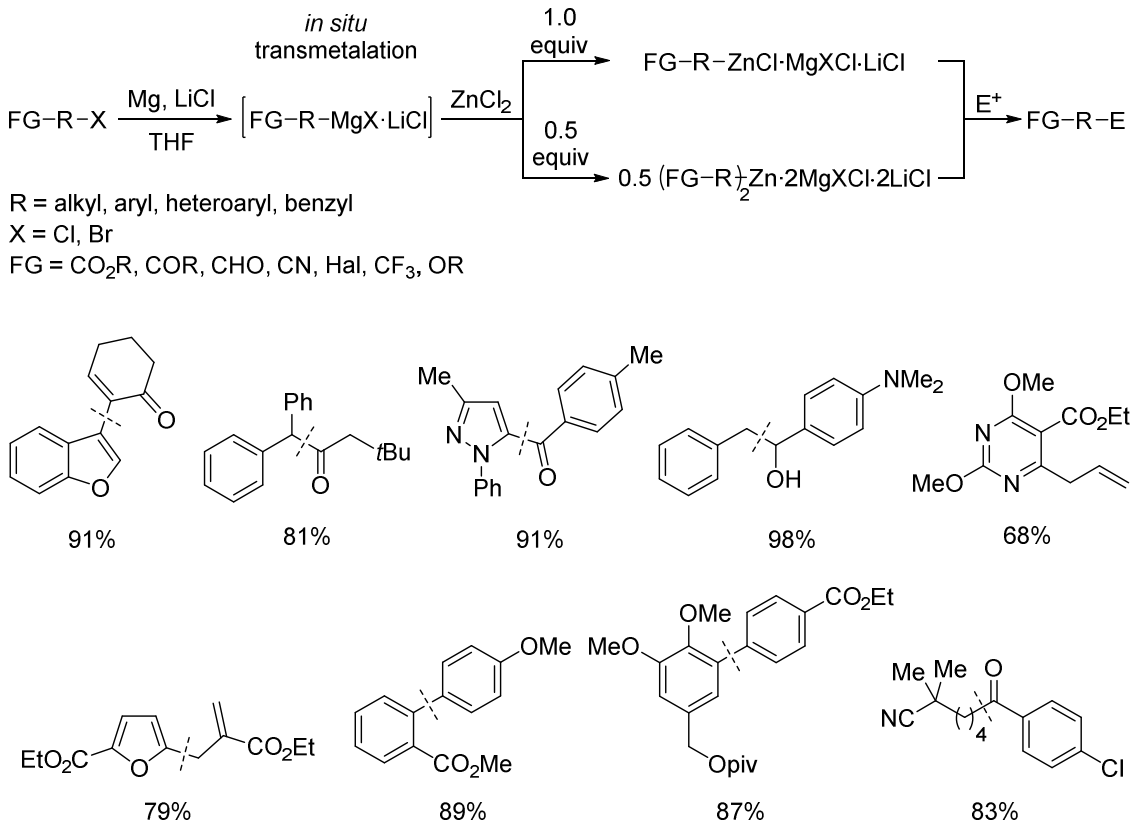
Scheme 15: LiCl-mediated preparation of functionalized organozinc reagents.

[55] a) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4324. b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

[56] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107. c) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.

The exact role of LiCl during the zinc insertion reaction was extensively studied by experimental, computational and analytical studies.[57] The obtained results designated that, on the one hand, LiCl reduces the energy of the transition state for the insertion,[57a] on the other hand, instead of forming organometallics of type R-ZnHal·LiCl, ESI-measurements indicate the active species to be an ate-complex of type Li^+R-ZnHalCl^-.[57b-c] Additionally, the solubility of the formed organometallic species in THF is increased leading to a free metal surface during the insertion reaction. This metal surface might be regenerated and thus, is available for the further reaction with the organic halide.

An alternative and further improved access to organozinc reagents displays the LiCl-mediated insertion of magnesium into organic halides in the presence of $ZnCl_2$, which has recently been disclosed by *Knochel* and co-workers (Scheme 16).[23,58]



Scheme 16: Preparation and reactivity of functionalized organozinc reagents using LiCl-mediated Mg-insertion in the presence of $ZnCl_2$.

Thus, oxidative addition of Mg in the presence of LiCl leads to a highly reactive organomagnesium reagent which is *in situ* trapped with 1.0 equivalents of $ZnCl_2$ to furnish a more stable zinc compound. The reactivity of the obtained zinc organyl may be

[57] a) C.-Y- Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780. b) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771. c) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

[58] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824. b) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.

enhanced by adding only 0.5 equivalents of $ZnCl_2$ and hence, preparing a diorganozinc species. Due to the higher reduction potential of magnesium, obvious advantages of this method consist in the shortened insertion times and in the possibility to employ "cheaper" (hetero)aryl bromides as well as heteroaryl chlorides as starting materials instead of the corresponding iodides (Scheme 16).[58]

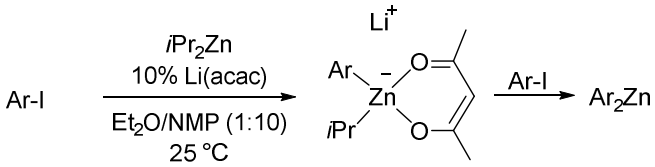
3.2 HALOGEN/ZINC EXCHANGE

Analogously to organomagnesium compounds, organozinc derivatives are also accessible *via* an exchange reaction. Formerly, *Furukawa* reported a successful I/Zn exchange using diethylzinc, but this reaction was restricted to 1,1-diiodoalkanes.[59] In 1992, *Knochel* and co-workers managed to readily convert a wide range of primary alkyl iodides to the corresponding dialkylzinc reagents upon treatment with Et_2Zn in the absence of solvent.[60] Nevertheless, this method suffered from several drawbacks including the necessity of elevated temperatures (50 – 60 °C) and excess of pyrophoric Et_2Zn (3.0 – 5.0 equiv) leading to scale-up problems. One year later, the same group reported an improved procedure employing copper(I) salts such as CuI and CuCN for catalyzing the I/Zn exchange and thus, leading to a twofold rate increase.[61] Yet, this strategy was still only applicable to primary alkyl iodides and the use of pyrophoric diethylzinc represented a major disadvantage. Hence, *Knochel* and *Micouin* developed a method for circumventing the use of neat and pyrophoric $i Pr_2Zn$ by the *in situ* generation of $i Pr_2Zn \cdot 2MgBr_2$ from *i*PrMgBr and $ZnBr_2$.[62] Thereby, they discovered that the additional salt $MgBr_2$ complexed to the thus-prepared $i Pr_2Zn$ leads to a rate acceleration of 200 times. Furthermore, the I/Zn exchange was not only restricted to primary alkyl iodides, but secondary derivatives could successfully be employed in the reaction sequence.[62]

This observation paved the way to the breakthrough in this field accomplished by *Knochel* and *Kneisel* in 2004, noticing that this I/Zn exchange can be catalyzed by the addition of catalytic amounts of Li(acac).[63] This lithium salt accelerated the rate of the I/Zn-exchange reaction even more than the aforementioned complexed magnesium salts, leading to a dramatically increased reactivity which, for the first time, made it possible to

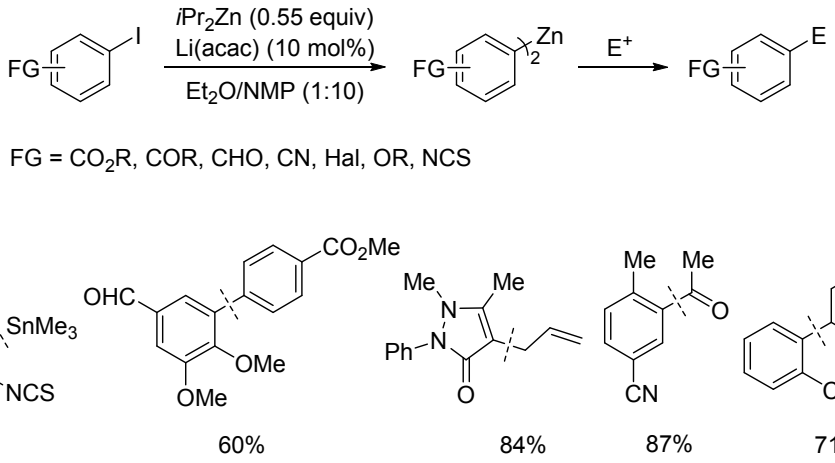
[59] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1966**, 3353. b) J. Furukawa, N. Kawabata, *Adv. Organomet. Chem.* **1974**, *12*, 83.
[60] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956.
[61] M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[62] L. Micouin, P. Knochel, *Synlett* **1997**, 327.
[63] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

even use aryl iodides as starting materials. This boost in reactivity is presumably attributed to the formation of an ate-intermediate displayed in Scheme 17.[63]



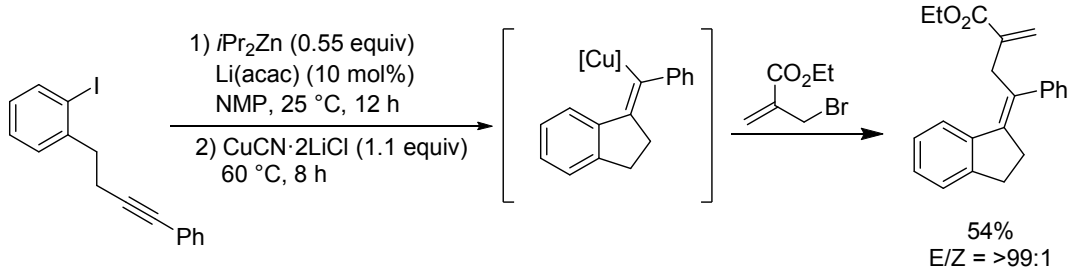
Scheme 17: Ate complex formed duing the Li(acac)-catalyzed iodine/zinc exchange using *i*Pr_2Zn.

Hence, highly functionalized (hetero)aryl iodides were successfully converted to the corresponding diarylzinc species and reacted with a wide range of electrophils, even tolerating sensitive aldehyde groups due to the mild reaction conditions used (Scheme 18).[63]



Scheme 18: Preparation and reactivity of functionalized zinc reagents by iodine/zinc exchange using *i*Pr_2Zn.

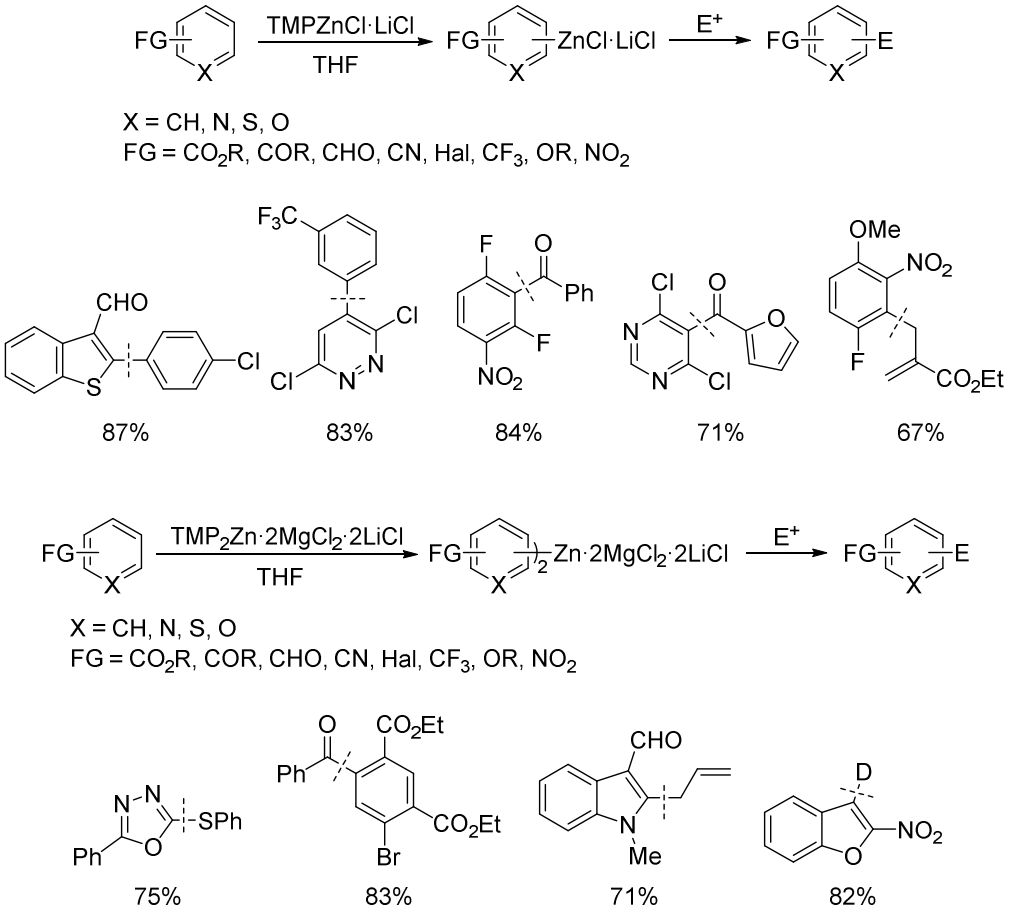
Moreover, this I/Zn exchange reaction could also be applied to an intramolecular carbocupration using CuCN·2LiCl stereoselectively yielding a carbocyclized derivative as *E*-isomer only (Scheme 19).[63]



Scheme 19: Carbocupration and cyclization by iodine/zinc exchange using *i*Pr_2Zn.

3.3 DIRECTED METALATION WITH AMIDE BASES

Hydrogen-metal interconversion displays a very "cheap" and convenient approach to organometallic intermediates. Great progress has been achieved with the development of the Turbo-*Hauser* bases TMPMgCl·LiCl[44] and $TMP_2Mg·2LiCl$.[45] However, sensitive aryl and heteroaryl derivatives bearing *e.g.* nitro and aldehyde substituents degradate upon treatment with these bases and thus, are excluded from magnesiation. To this end, *Knochel* developed the extremely mild bases TMPZnCl·LiCl[64] and $TMP_2Zn·2MgCl_2·2LiCl$[65] allowing the chemoselective zincation of sensitive substrates. Consequently, a wide range of sensitive aromatic and heteroaromatic derivatives could be smoothly zincated and subsequently reacted with various electrophiles to afford polyfunctional (hetero)arenes (Scheme 20).[46]



Scheme 20: Direct zincation using TMPZnCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$.

[64] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406. c) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680. d) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584.

[65] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705. c) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, *47*, 6387.

4. 7-AZAINDOLE AND ITS CHEMISTRY

4.1 BACKGROUND AND APPLICATIONS OF 7-AZAINDOLES

Azaindoles, also called pyrrolopyridines, display *N*-heterocyclic compounds of key importance and may be described as indole bioisosters[66] containing an additional nitrogen atom in the 6-membered ring (position 4-7). Consequently, these heterocycles are built up from an electron-rich pyrrole and an electron-deficient pyridine subunit. Depending on the position of the additional nitrogen in the pyridine ring, these heterocycles are categorized as 4-, 5-, 6- or 7-azaindoles (Figure 1).[67]

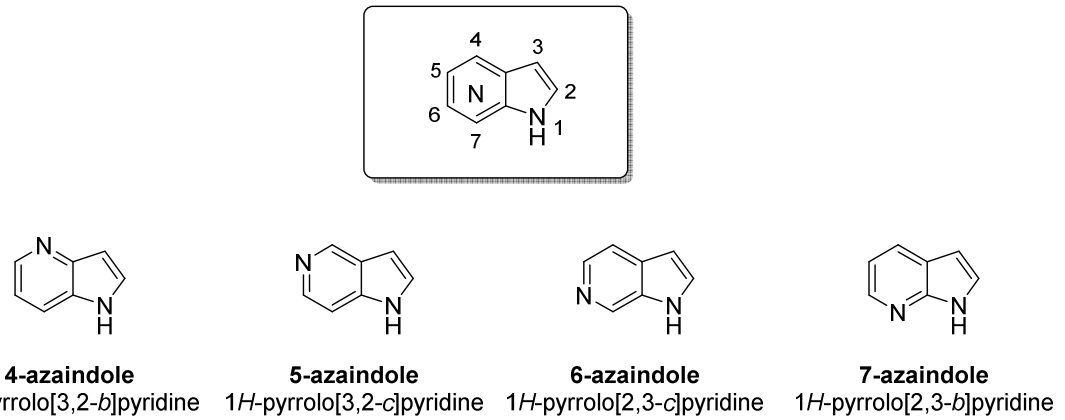


Figure 1: The four isomeric systems of azaindoles (pyrrolopyridines).

Among the four isomeric systems of azaindoles, the 7-azaindole core is the most popular one and has first been isolated from coal tar in 1943 by *Kruber*.[68] Compared to the related indoles, the natural occurance of azaindoles is rather scarce. However, the 7-azaindole skeleton can be found as motif in some natural products, and by far the most famous example for these is the class of variolins isolated 20 years ago from the Antarctic marine sponge *Kirkpatrickia variolosa* (Figure 2).[69]

[66] a) J.-Y. Mérour, B. Joseph, *Curr. Org. Chem.* **2001**, *5*, 471. b) A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph, L. Meijer, *J. Med. Chem.* **2008**, *51*, 737. c) D. P. Power, O. Lozach, L. Meijer, D. H. Grayson, S. Connon, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4940.

[67] J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, C. H. Senanayake, *Chem. Soc. Rev.* **2007**, *36*, 1120.

[68] O. Kruber, *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 128.

[69] a) N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin, H. Hope, *Tetrahedron* **1994**, *50*, 3987. b) G. Trimurtulu, J. D. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, G. B. Jameson, *Tetrahedron* **1994**, *50*, 3993.

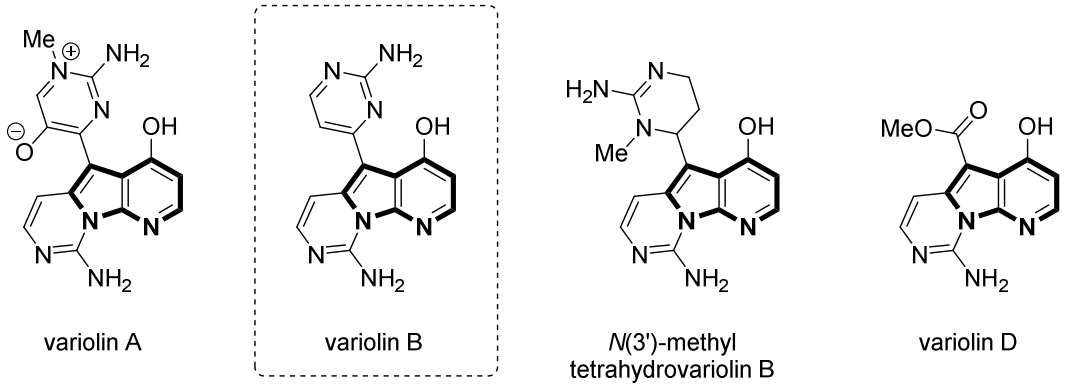


Figure 2: The class of variolins.

These alkaloids are known to posses antibacterial, antiviral and, in particular in case of variolin B, antitumor properties.[69] Thus, variolin B inhibits the growth of the P388 tumor cell line and is active against *Herpes simplex* and *polio virus*, while its related derivative methyltetrahydrovariolin B shows cytotoxical activity against human colon tumor cells and *Saccharomyces cerevisiae*.[69,70]

Another essential class of 7-azaindole containing natural products are displayed by meriolins[71] which show structural similarities to variolins. Yet, instead of a pyrimidyl-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine skeleton like variolins, they are built up from a pyrimidyl-substituted 7-azaindole core.[72] These meriolins indeed show an even higher cytotoxical potential than variolins,[71,72] and it is not surprising that within the last two decades the biological and pharmacological interest in 7-azaindoles has dramatically risen. Thus, these *N*-heterocycles became one of the most promising building blocks in pharmaceutical and agrochemical industries,[66,73] giving rise to

[70] a) D. Fernandez, A. Ahaidar, G. Danelon, P. Cironi, M. Marfil, O. Perez, C. Cuevas, F. Albericio, J. A. Joule, M. Alvarez, *Monatsh. Chem.* **2004**, *135*, 615. b) P. M. Fresneda, S. Delgado, A. Francesch, I. Manzanares, C. Cuevas, P. Molina, *J. Med. Chem.* **2006**, *49*, 1217.

[71] a) K. Bettayeb, O. M. Tirado, S. Marionneau-Lambot, Y. Ferandin, O. Lozach, J. C. Morris, S. Mateo-Lozano, P. Drückes, C. Schächtele, M. Kubbutat, F. Liger, B. Marquet, B. Joseph, A. Echalier, J. Endicott, V. Notario, L. Meijer, *Cancer Res.* **2007**, *67*, 8325. b) A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clement, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. Endicott, B. Joseph, L. Meijer, *J. Med. Chem.* **2008**, *51*, 737.

[72] S. R. Walker, E. J. Carter, B. C. Huff, J. C. Morris, *Chem. Rev.* **2009**, *109*, 3080.

[73] For reviews, see: a) F. Popowycz, S. Routier, B. Joseph, J.-Y. Mérour, *Tetrahedron* **2007**, *63*, 1031. b) *Modern Heterocyclic Chemistry*, Vol. 4 (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), WILEY-VCH, Weinheim, **2011.** c) *Bioactive Heterocyclic Compound Classes*, Vol. 1 (Eds.: C. Lamberth, J. Dinges), WILEY-VCH, Weinheim, **2012.** d) Z. Wang, X. Wang, *Prog. Chem.* **2012**, *24*, 1974. e) J.-Y. Mérour, S. Routier, F. Suzenet, B. Joseph, *Tetrahedron* **2013**, *69*, 4767.

valuable cytotoxical targets for the development of *e.g.* anti-inflammatory,[74] anti-cancer[75] and anti-psychotic[76] therapeutics (Figure 3).

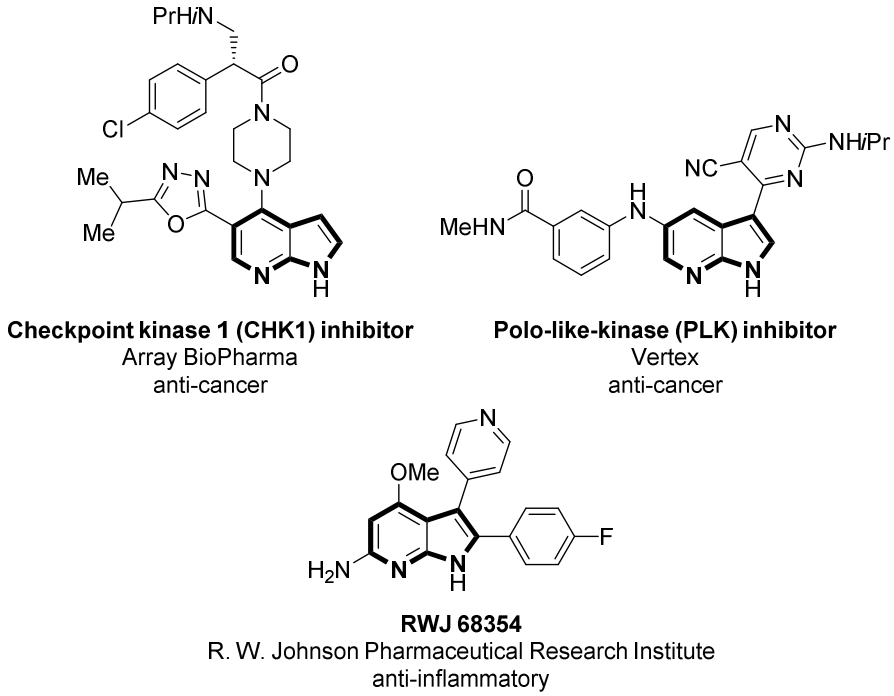


Figure 3: Examples of pharmaceutically important 7-azaindoles.

Furthermore, due to their unique electronic behaviour combining opposite electronic features of the two fused heterocycles (pyridine = electron-poor/hydrogen-bond acceptor; pyrrole = electron-rich/hydrogen-bond donor) on one heteroaromatic skeleton, 7-azaindoles have also found broad application as organic light emitting diodes (OLEDS),[77] luminescent molecules[78] and ligands.[79]

4.2 SYNTHESES OF 7-AZAINDOLES

Exactly the aforementioned electronic properties differentiate (7-)azaindoles from their structurally related indoles to such extend, that common synthetic strategies for the construction or the design of indoles,[80] such as the *Fischer*, *Madelung* or *Reissert*

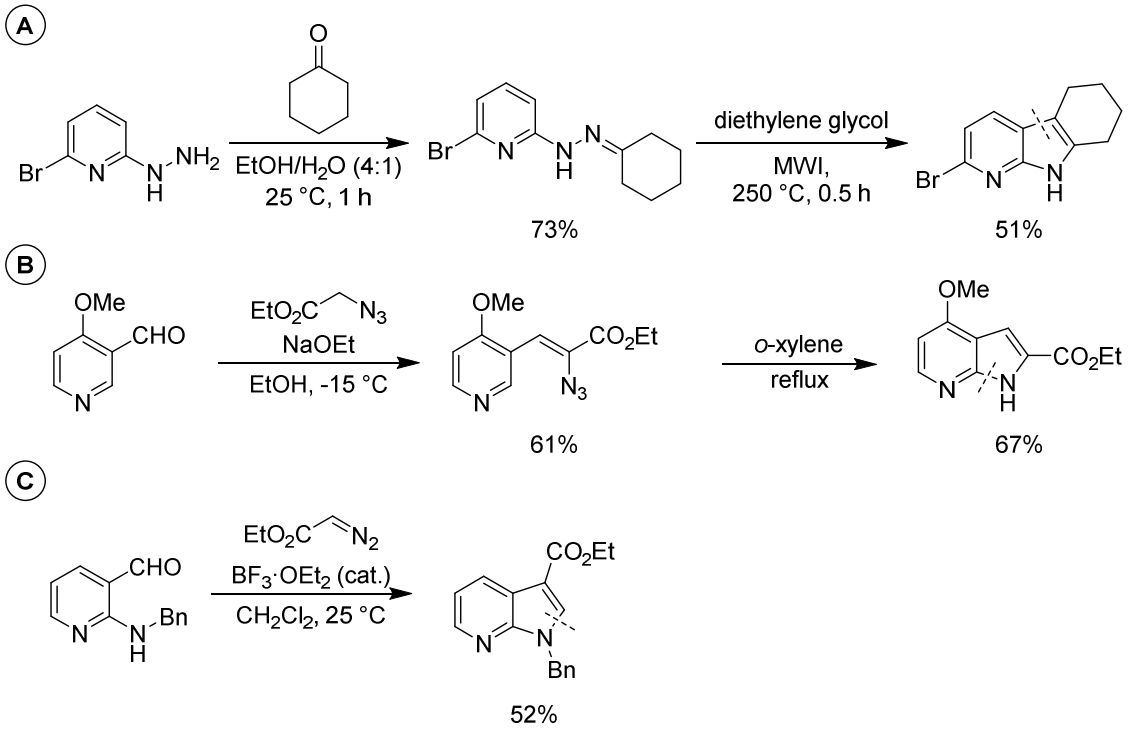
[74] J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, B. Fahmy, G. C. Olini, J. E. Davis, J. L. Pellegrino-Gensey, P. H. Schäfer, J. J. Siekierka, *J. Med. Chem.* **1998**, *41*, 4196.
[75] a) J. Blake (Array BioPharma Inc.), WO 2009/089352, **2009**. b) M. Mortimore (Vertex Pharmaceuticals Inc.), WO2008/079346, **2008**. c) T. Heinrich (Merck GmbH), WO 2006/114180, **2006**.
[76] J. J. Kulagowski, H. B. Broughton, N. R. Curtis, I. M. Mawer, M. P. Ridgill, R. Baker, F. Emms, S. B. Freedman, R. Marwood, S. Patel, S. Patel, C. I. Ragan, P. D. Leeson, *J. Med. Chem.* **1996**, *39*, 1941.
[77] J. S. Hong, H. S. Shim, T.-J. Kim, Y. Kang, *Tetrahedron* **2007**, *63*, 8767.
[78] a) Q. Wu, M. Estaghamatian, N.-X. Hu, Z. Popovic, G. Enright, S. R. Breeze, S. Wang, *Angew. Chem. Int. Ed.* **1999**, *38*, 985. b) Q. Wu, A. Hook, S. Wang, *Angew. Chem. Int. Ed.* **2000**, *39*, 3933. c) For a review, see: S.-B. Zhao, S. Wang, *Chem. Soc. Rev.* **2010**, *39*, 3124.
[79] C. Waloch, J. Wieland, M. Keller, B. Breit, *Angew. Chem. Int. Ed.* **2007**, *46*, 3037.
[80] For a recent review on indole synthesis, see: G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875 and references cited therein.

synthesis, are not well adaptable to their aza-analogues.[67] Since naturally occurring 7-azaindoles are rare, most derivatives are synthetic products making a sophisticated approach to such heterocycles indispensable. However, due to the electron-poor nature of the pyridine ring, the synthesis of azaindoles often bears certain challenges.

4.2.1 Syntheses of 7-Azaindoles Starting from Pyridine Derivatives

The most convenient approach to azaindoles consists in the formation of the pyrrole ring starting from substituted pyridine derivatives.[67]

Unfortunately, the *Fischer* cyclization[81] as one of the classical indole formation strategies cannot directly be translated to the synthesis of azaindoles, since pyridyl derived hydrazines need harsher conditions limiting the substrate scope dramatically and often resulting in only modest yields.[66a,67,73a] Yet, while the group of *Suzenet* easily managed the formation of 4- and 6-azaindoles *via* the *Fischer* pathway,[82] the synthesis of 7-azaindoles proved to be more difficult.[73e] Still, it could be realized by *Kroth et al.* under microwave irradiation (MWI) in moderate to good yields (Scheme 21; **A**).[83]

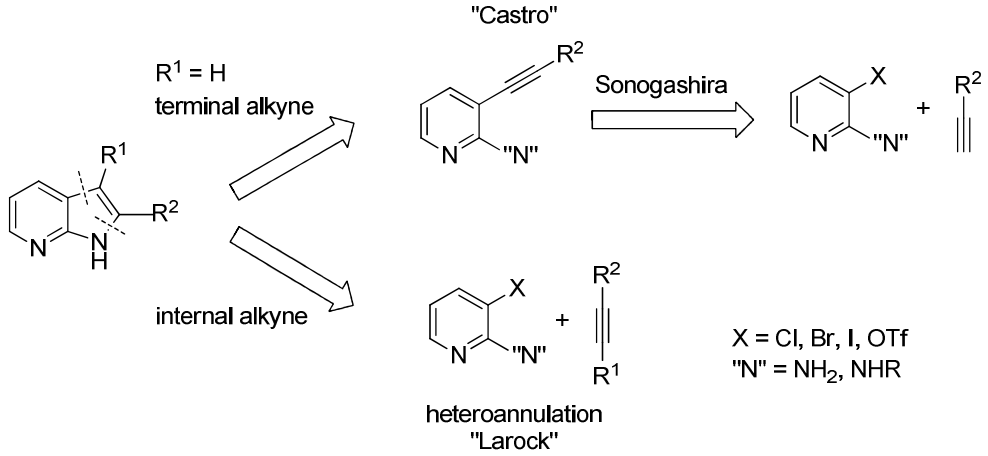


Scheme 21: *Fischer* cyclization (**A**), *Hemetsberger* reaction (**B**) and *Hossain* reaction (**C**) for the syntheses of 7-azaindoles.

[81] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. b) For a review, see: M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29.
[82] M. Jeanty, J. Blu, F. Suzenet, G. Guillaumet, *Org. Lett.* **2009**, *11*, 5142.
[83] H. Kroth (AC Immune S.A.), WO 2011/128455, **2011**.

Furthermore, *Fresneda* and *Molina* were the first to successfully adapt the *Hemetsberger* reaction,[84] another straightfoward route to indoles, to the synthesis of 7-azaindole compounds (Scheme 21; **B**).[85] Similarly, *Fournier* and co-workers managed to prepare 7-azaindoles from 2-(*N*-benzylamino)-3-formylpyridine according to *Hossain*'s indole[86] synthesis (Scheme 21; **C**).[87]

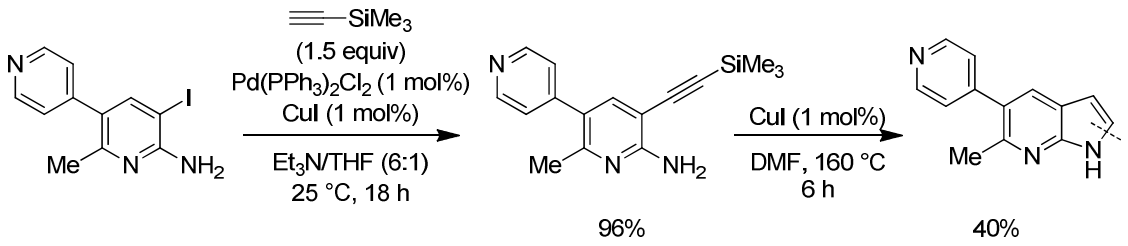
Analogously to the construction of indoles, for the assembly of azaindoles, organometallic strategies proved to be extremely useful. In this context, especially palladium catalysis plays a key role in the synthesis of 7-azaindoles, and besides *Heck*,[88,89] *Suzuki*[90,91] and *Stille*[92,93] reactions, cross-couplings of *ortho*-aminohalopyridines with terminal (two-step process; *Castro*-synthesis)[94] or internal alkynes (one-step process; *Larock*-annulation)[95] constitute one of the main approaches to these heterocycles (Scheme 22).[67]



Scheme 22: Pd-catalyzed approaches to 7-azaindoles involving internal and terminal alkynes.

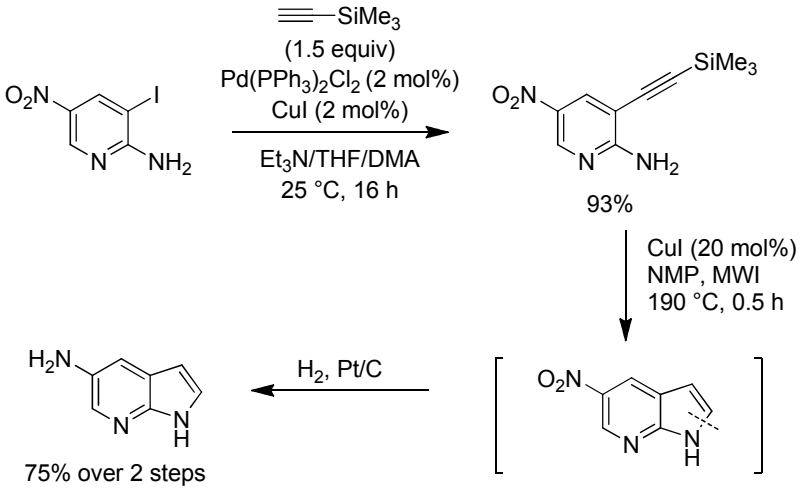
[84] H. Hemetsberger, D. Knittel, *Monatsh. Chem.* **1972**, *103***,** 194.
[85] P. M. Fresneda, P. Molina, S. Delgado, J. A. Bleda, *Tetrahedron Lett.* **2000**, *41*, 4777.
[86] M. E. Dudley, M. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M.-R. Atuu, B. Branstetter, M. M. Hossain, *J. Org. Chem.* **2004**, *69*, 7599.
[87] P. Levesque, P.-A. Fournier, *J. Org. Chem.* **2010**, *75*, 7033.
[88] a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518. b) For an early review, see: R. F. Heck, *Org. React.* **1982**, *27*, 345.
[89] For the use of *Heck*-type reactions in the synthesis of 7-azaindoles, see: N. Lachance, M. April, M. A. Joly, *Synthesis* **2005**, 2571.
[90] a) N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866. b) For an early review, see: A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749.
[91] For the use of *Suzuki*-type reactions in the synthesis of 7-azaindoles, see: V. Kumar, J. A. Dority, E. R. Bacon, B. Singh, G. Y. Lesher, *J. Org. Chem.* **1992**, *57*, 6995.
[92] a) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636. b) For an early review, see: T. N. Mitchell, *J. Organomet. Chem.* **1986**, *304*, 1.
[93] For the use of *Stille*-type reactions in the synthesis of 7-azaindoles, see: T. Sakamoto, C. Satoh, Y. Kondo, H. Yamanaka, *Heterocycles* **1992**, *34*, 2379.
[94] C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071.
[95] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689. b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652. c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.

Applying the *Castro*-sequence[94] for the construction of 7-azaindoles, the first step involves a *Sonogashira* cross-coupling[96] of an *ortho*-aminohalopyridine with a terminal alkyne. Thereby, the aminopyridine may either be unprotected or substituted with different groups such as *tert*-butyloxycarbonyl(Boc)-, tosylate(Ts)- or alkyl-moieties. The thus-obtained alkynyl pyridine is then subjected to a cyclization reaction mainly performed under Cu(I)-catalysis or base-promotion. For example, the group of *Kumar* reported the *Sonogashira* coupling of a polyfunctional iodopyridine with TMS-acetylene followed by Cu-catalyzed cyclization of the thus-obtained alkyne to a 7-azaindole scaffold (Scheme 23).[97] The low yield is attributed to the loss of the TMS-goup either during the reaction or during the aqueous work-up.



Scheme 23: CuI-catalyzed synthesis of a 7-azaindole.

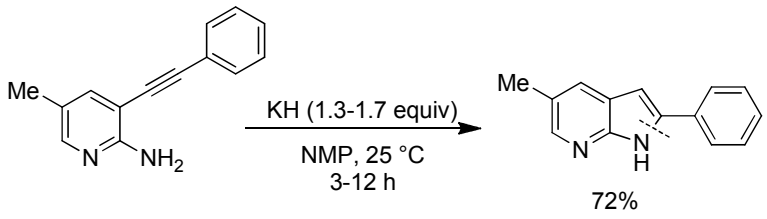
An improvement of this Cu(I)-catalyzed ring closing reaction was achieved by *Pearson* developing a route alternative to the *Robison*[98] approach for the synthesis of 5-amino-7-azaindole.[99] Thereby, ring closure was achieved under microwave irradiation (Scheme 24).



Scheme 24: Cu(I)-catalyzed **s**ynthesis of a 7-azaindole under microwave irradiation.

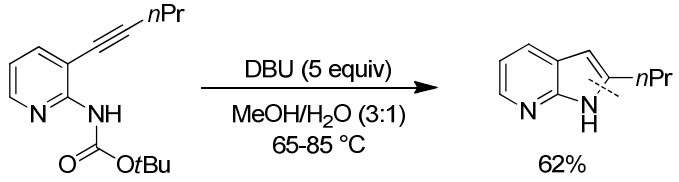
[96] a) K. Sonogashira, Y. Thoda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467. b) F. Monnier, F. Turtaut, L. Duroure, M. Taillefer, *Org. Lett.* **2008**, *10*, 3203. c) C. He, J. Ke, H. Xu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 1527.
[97] V. Kumar, J. A. Dority, E. R. Bacon, B. Singh, G. Y. Lesher, *J. Org. Chem.* **1992**, *57*, 6995.
[98] M. M. Robison, B. L. Robison, F. P. Butler, *J. Am. Chem. Soc.* **1959**, *81*, 743.
[99] S. E. Pearson, S. Nandan, *Synthesis*, **2005**, 2503.

However, the examples shown above clearly indicate that ring closing reactions achieved with Cu-catalysts usually require rather harsh conditions. Another, milder protocol for the cyclization would therefore be highly desirable. To this end, base-promotion displays a valuable alternative, which has recently been proven by *Knochel* and co-workers employing bases like potassium hydride and cesium *tert*-butoxide in *N*-methylpyrrolidin-2-one (NMP) to smoothly convert an alkyne-substituted aminopyridine to the appropriate 7-azaindole derivative 72% yield (Scheme 25).[100]



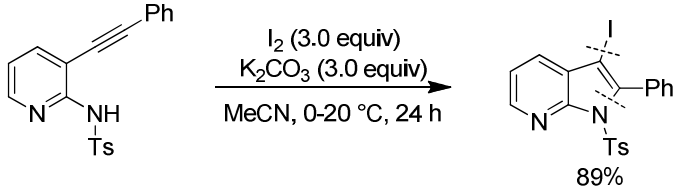
Scheme 25: Potassium hydride-promoted synthesis of a 7-azaindole.

More recently, *Riether* and co-workers described the mild cyclization of *N*-Boc-protected alkynylated pyridines mediated by 1,8-diazabicycloundec-7-ene (DBU) for the synthesis of unprotected 7-azaindoles (Scheme 26). Noteworthy, the Boc-protection was crucial in this reaction sequence, since unprotected aminopyridines did not yield the desired fused heterocycles under these conditions.



Scheme 26: Synthesis of a 7-azaindole *via* DBU-promotion.

Another modification of the method involving terminal alkynes was achieved by *Knight* describing the construction of a 2-substituted 3-iodo-7-azaindole *via* an iodocyclization process employing a tosylate-protected alkyne to furnish a 3-iodinated heterocycle (Scheme 27).[101]

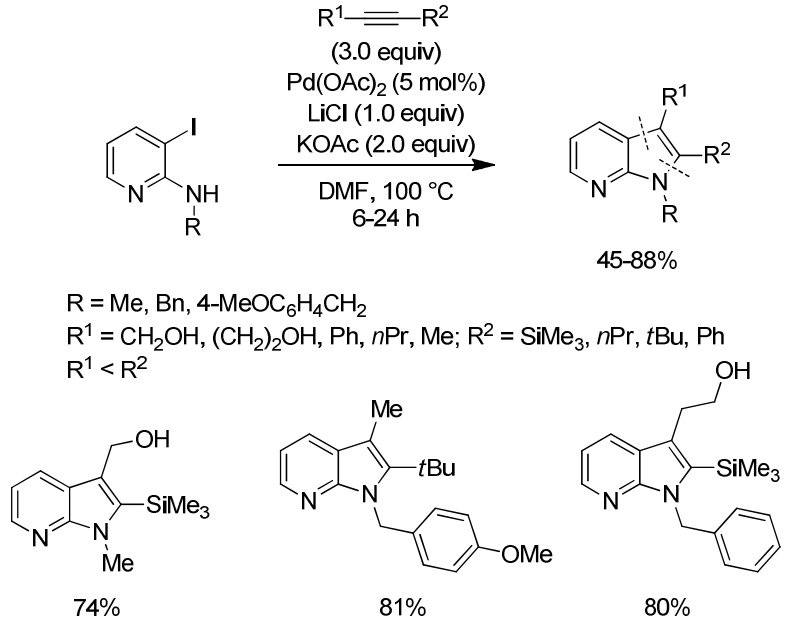


Scheme 27: Synthesis of a 7-azaindole *via* iodocylization.

[100] C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571.
[101] M. Amjad, D. W. Knight, *Tetrahdron Lett.* **2004**, *45*, 539.

The *Larock* indole[95] synthesis, involving the palladium-catalyzed annulation of terminal alkynes (see Scheme 22), is one of the most valuable pathways for the construction of indoles and has found applications in the synthesis of 7-azaindoles, as well. If the alkyne substitutents are adequately different, these reactions usually proceed with high regioselectivities having the bulkiest group ending up in the C2-position of the (aza)indole core.[67]

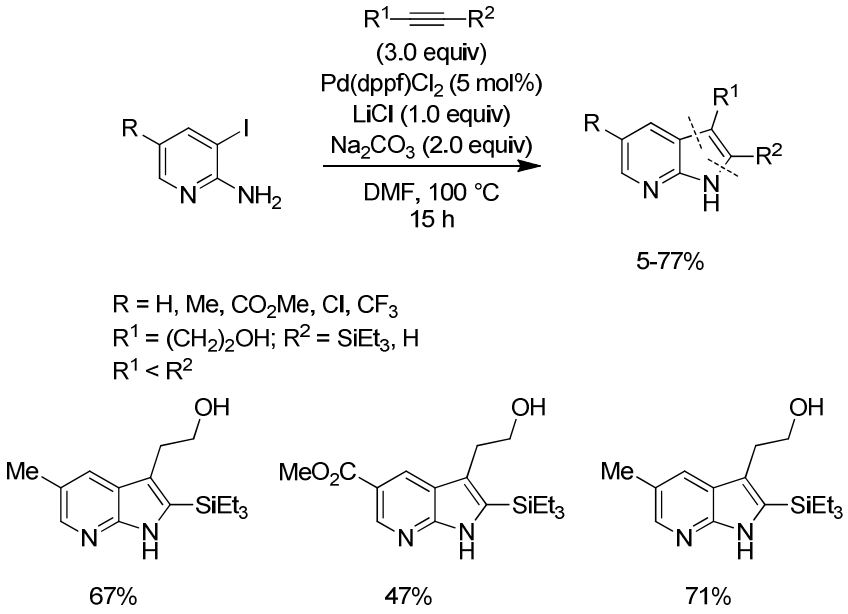
Already in 1998, *Yum et al.* described the smooth construction of 2,3-substituted 7-azaindoles by reaction of N1-protected pyridines with internal alkynes (Scheme 28).[102] In this context, they discovered that 1) the addition of LiCl dramatically increases the yields, and 2) the presence and the nature of the protecting group attached to the N1-atom is crucial for a successful conversion. Thus, the absence of substituents on N1 or protecting groups such as acetyl-, pivaloyl- and Boc-moieties led either to no reaction at all or to very low yields of cyclized product, while protective groups such as alkyl or benzyl substituents guaranteed good results.[102]



Scheme 28: Syntheses of 7-azaindoles *via Larock* heteroannulation of N1-protected aminopyridines.

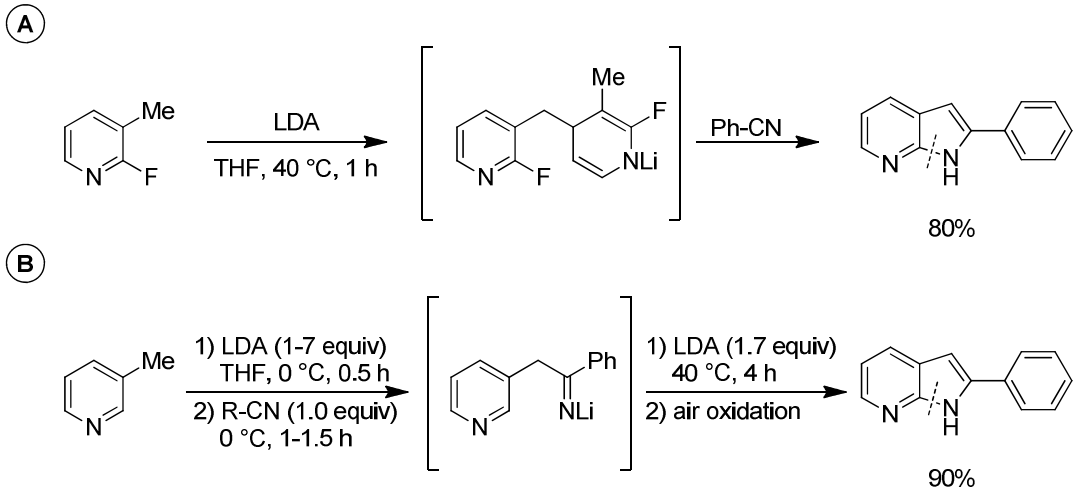
A progress in this field could be achieved by *Ujjainwalla* and co-workers managing to use unprotected *ortho*-aminoiodopyridines in the presence of $Pd(dppf)Cl_2$ (dppf = (diphenylphosphino)ferrocene) to prepare 2,3,5-substituted 7-azaindoles by *Larock*-heteroannulation with internal alkynes (Scheme 29).[103]

[102] S. Park, J.-K. Choi, E. K. Yum, D.-C. Ha, *Tetrahedron Lett.* **1998**, *39*, 627.
[103] F. Ujjainwalla, D. Warner, *Tetrahedron Lett.* **1998**, *39*, 5355.



Scheme 29: Syntheses of 7-azaindoles *via Larock* synthesis of N1-uprotected amino pyridines.

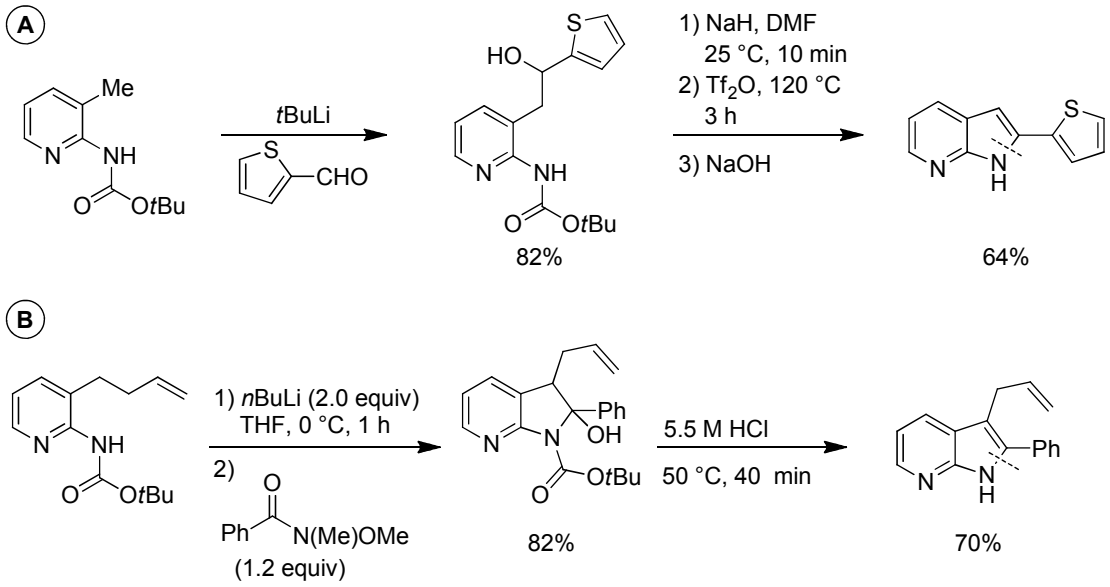
Organolithium-based strategies display another useful organometallic approach to 7-azaindoles. Thus, in 2008, *Collum* and co-workers reported the successful synthesis of a 7-azaindole *via* the *Chichibabin* cyclization starting from 2-fluoro-3-picoline (Scheme 30; **A**).[104] Similarly, when 3-picoline, bearing no fluorine substitutent in the 2-position, is treated with lithium *N*,*N*-di*iso*propylamide (LDA)[105] and reacted with a nitrile, the corresponding 2-substituted 7-azaindole was obtained after oxidation during work-up (Scheme 30; **B**).[106]



Scheme 30: Organolithium-based strategies for the syntheses of 7-azaindoles starting from 3-picolines.

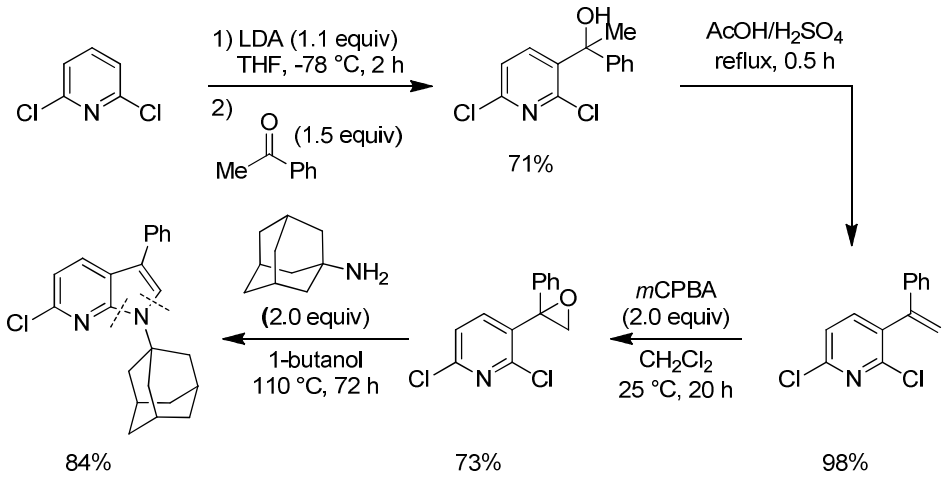
[104] Y. Ma, S. Breslin, I. Keresztes, E. Lobkovsky, D. B. Collum, *J. Org. Chem.* **2008**, *73*, 9610.
[105] a) M. Hammell, R. Levine, *J. Org. Chem.* **1950**, *15*, 162. b) For a recent review, see: D. B. Collum, A. J. McNeil, A. Ramirez, *Angew. Chem. Int. Ed.* **2007**, *46*, 3002.
[106] M. L. Davis, B. J. Wakefield, J. A. Wardell, *Tetrahedron* **1992**, *48*, 939.

Furthermore, these heterocycles are also available by lithiation of Boc-protected 2-aminopicoline and subsequent quenching with an aldehyde to afford a 2-arylated and N1-unprotected 7-azaindole after cyclization (Scheme 31; **A**).[107] When the 3-methyl group of such Boc-protected aminopyridines was modified with other substituents, treatment with *n*BuLi[108] and subsequent trapping with DMF or *Weinreb* amides furnished 2,3-substituted 7-azaindoles (Scheme 31; **B**).[109]



Scheme 31: Organolithium-based strategies for the syntheses of 7-azaindoles.

A lithiation-based approach to 7-azaindoles could as well be accomplished involving 2,6-dichloropyridine demonstrated by *Schirok* (Scheme 32).[110]

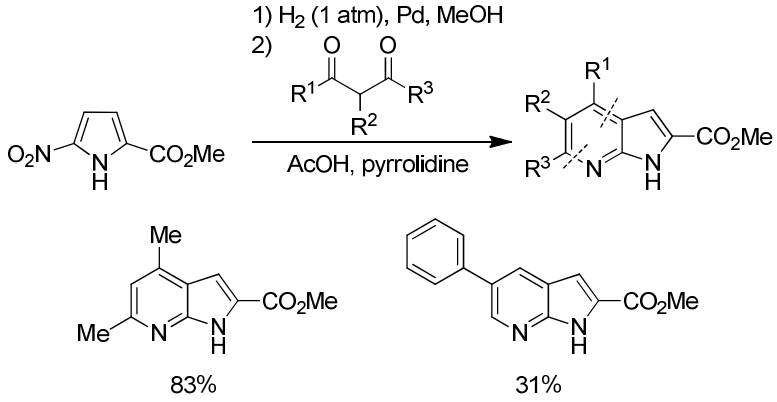


Scheme 32: Organolithium-based strategy for the synthesis of a 7-azaindole.

[107] J. Parcerisa, M. Romero, M. D. Pujol, *Tetrahedron* **2008**, *64*, 500.
[108] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, 61, 109.
[109] D. Hands, B. Bishop, M. Cameron, J. S. Edwards, I. F. Cottrell, S. H. B. Wright, *Synthesis* **1996**, 877.
[110] H. Schirok, *Synlett* **2005**, 1255.

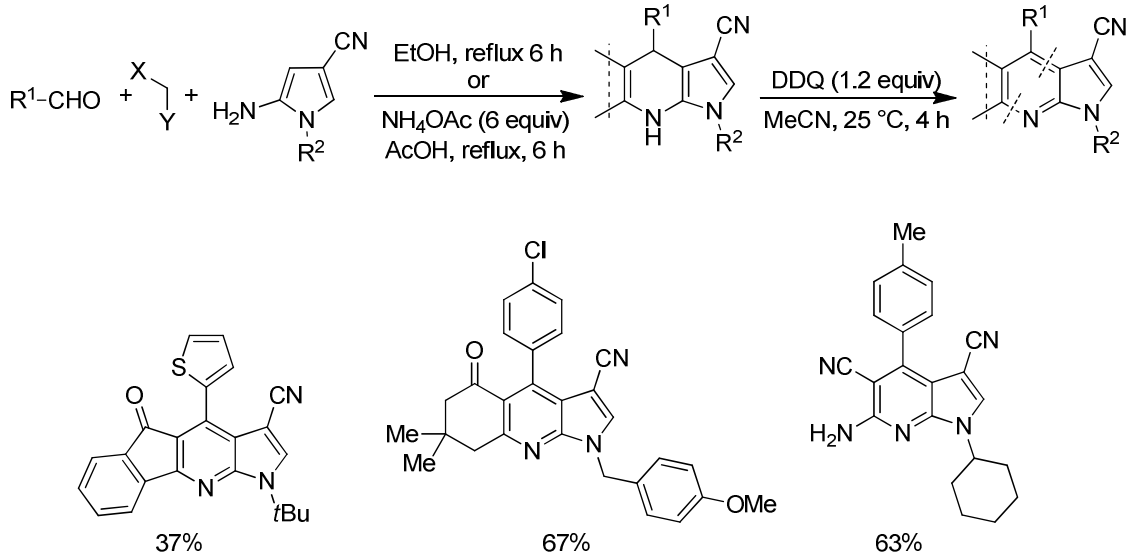
4.2.2 SYNTHESES OF 7-AZAINDOLES STARTING FROM PYRROLE DERIVATIVES

Besides the more common approach to use substituted pyridine derivatives to construct the pyrrole ring, few examples are reported for the formation of 7-azaindoles through pyrrole precursors. Nevertheless, the group of *Cuny* described the synthesis of 7-azaindole derivatives by reduction of methyl 5-nitropyrrole-2-carboxylate and subsequent reaction with dicarbonyl derivatives (Scheme 33).[73d,111]



Scheme 33: Syntheses of 7-azaindoles starting from a nitropyrrole.

Furthermore, in 2012, *Iaroshenko* reported the three-component synthesis of several polyfunctionalized 7-azaindoles (Scheme 34).[112]



Scheme 34: Syntheses of 7-azaindoles starting from an aminopyrrole.

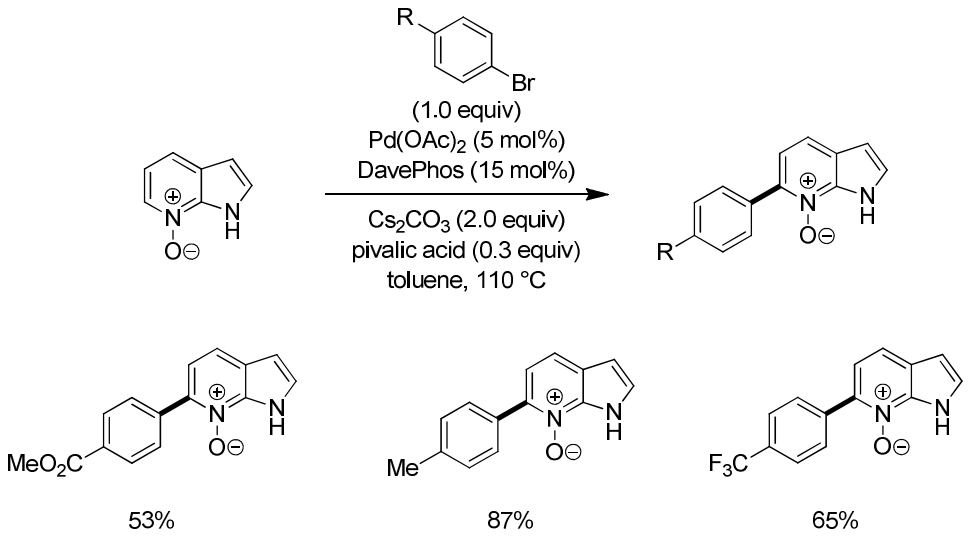
[111] J. Wu, X. Xing, G. D. Cuny, *Lett. Org. Chem.* **2009**, *6*, 203.
[112] M. Vilches-Herrera, I. Knepper, N. de Souza, A. Villinger, V. Y. Sosnovskikh, V. O. Iaroshenko, *ACS Comb. Sci.* **2012**, *14*, 434.

Thereby, the formation of the azaindole core involved the *Knoevenagel* reaction between different benzaldehydes and activated methylene compounds (X-CH_2-Y) followed by Michael addition of an amino pyrrole on the *Knoevenagel* adduct to furnish dihydroazaindoles which were subsequently oxidized leading to the corresponding polysubstituted heteroaromatics (Scheme 34).[112]

4.3 REACTIONS OF 7-AZAINDOLES

4.3.1 FUNCTIONALIZATION OF POSITION 6 OF THE 7-AZAINDOLE SCAFFOLD

Most methods applied for C6-functionalization of the 7-azaindole scaffold involved the use of *N*-oxides, which were usually obtained upon treatment of the azaindole derivatives with *meta*-chloroperoxybenzoic acid (*m*CPBA).[113] These *N*-oxide derivatives were then reacted, for example, with aryl bromides under Pd-catalysis to afford the 6-arylated *N*-oxides (Scheme 35).

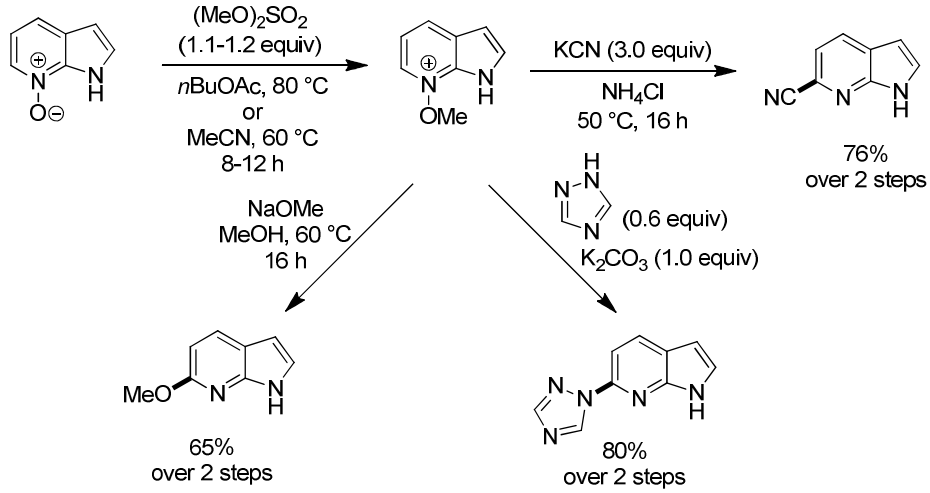


Scheme 35: C6-functionalization starting from *N*-oxides.

In 2008, *Storz*[114] described an even more elegant approach to 6-substituted 7-azaindoles involving *N*-oxide compounds and thus, greatly improved a previously described procedure for the C6-functionalization of 7-azaindoles developed by *Ohshiro*.[115] Thereby, an *N*-oxide derivative was smoothly transformed to the corresponding *O*-methyl compound by treatment with dimethyl sulfate without methylation occurring on the pyrrole nitrogen or on C3 of the *N*-oxide salt. These *O*-methyl compounds reacted with various nucleophiles in an addition-elimination process

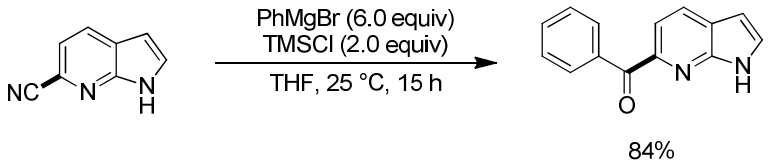
[113] C. Pillard, C. E. Bassène, F. Suzenet, G. Guillaumet, *Synthesis* **2008**, 2049.
[114] T. Storz, M. D. Bartberger, S. Sukits, C. Wilde, T. Soukup, *Synthesis* **2008**, 201.
[115] S. Minakata, M. Komatsu, Y. Ohshiro, *Synthesis* **1992**, 661.

under the appropriate conditions to furnish a wide range of 6-functionalized 7-azaindoles (Scheme 36).[114]



Scheme 36: C6-functionalization starting from *N*-*O*-methyl derivatives.

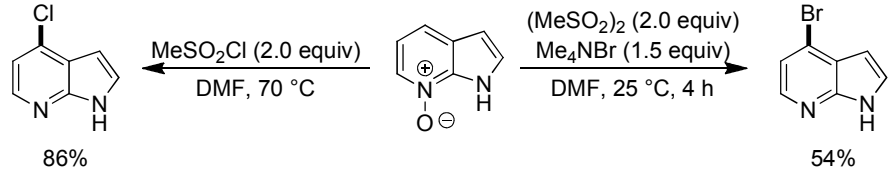
Noteworthy, the thus-obtained 6-cyano-7-azaindole displayed a valuable intermediate for further modifications, and its treatment with PhMgBr in THF furnished the corresponding ketone (Scheme 37).[113]



Scheme 37: C6-functionalization starting from 6-cyano-7-azaindole.

4.3.2 FUNCTIONALIZATION OF POSITION 4 OF THE 7-AZAINDOLE SCAFFOLD

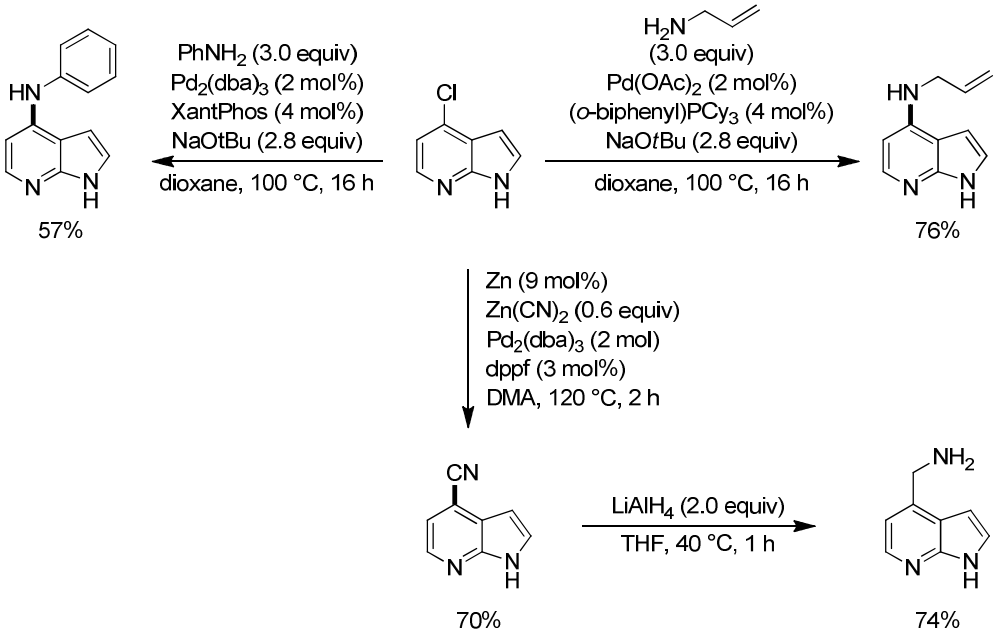
The C4-functionalization of the 7-azaindole core is challenging and most approaches make use of the aforementioned azaindole *N*-oxide derivatives, which proved to be quite useful for functionalization of position 6, as well. In this context, *Thibault* and co-workers subjected 7-azaindole *N*-oxide to chlorination and bromination to furnish the appropriate 4-halo derivatives (Scheme 38).[116]



Scheme 38: C4-functionalization starting from7-azaindole *N*-oxide.

[116] C. Thibault, A. L'Heureux, R. S. Bhide, R. Ruel, *Org. Lett.* **2003**, *5*, 5023.

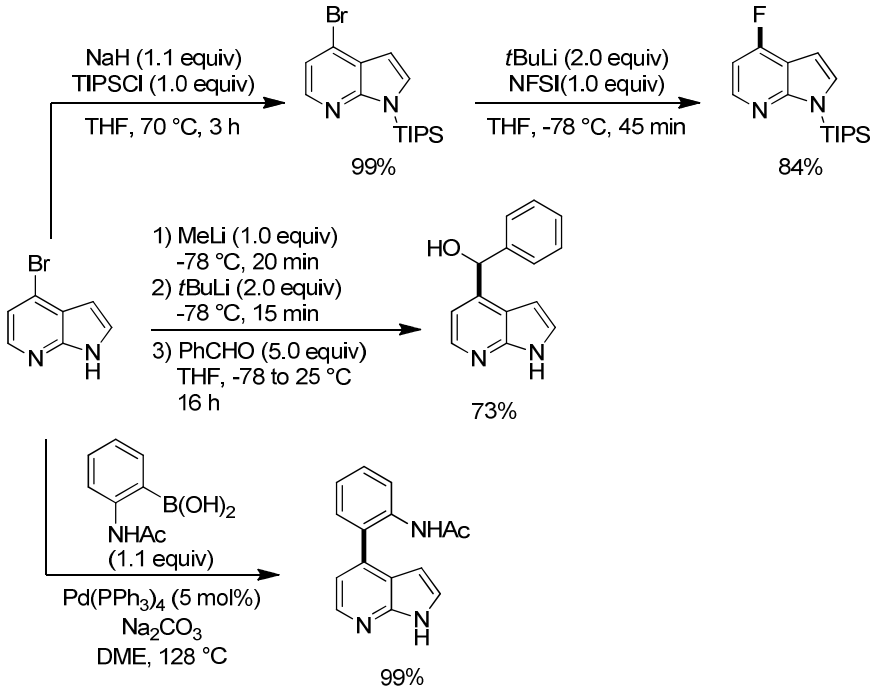
The thus-otbained heterocycles display useful substrates for further modifications. The chloro derivative (Scheme 38) readily reacted with amines *via Buchwald*-type Pd-catalyzed aminations to give the corresponding 4-amino heterocycles.[116,117] Moreover, 4-chloro-7-azaindole was treated with $Zn(CN)_2$ in the presence of $Pd_2(dba)_3$ to afford a nitrile which was subsequently reduced with $LiAlH_4$ to afford an aminomethyl azaindole (Scheme 39).[118]



Scheme 39: C4-functionalization starting from 4-chloro-7-azaindole.

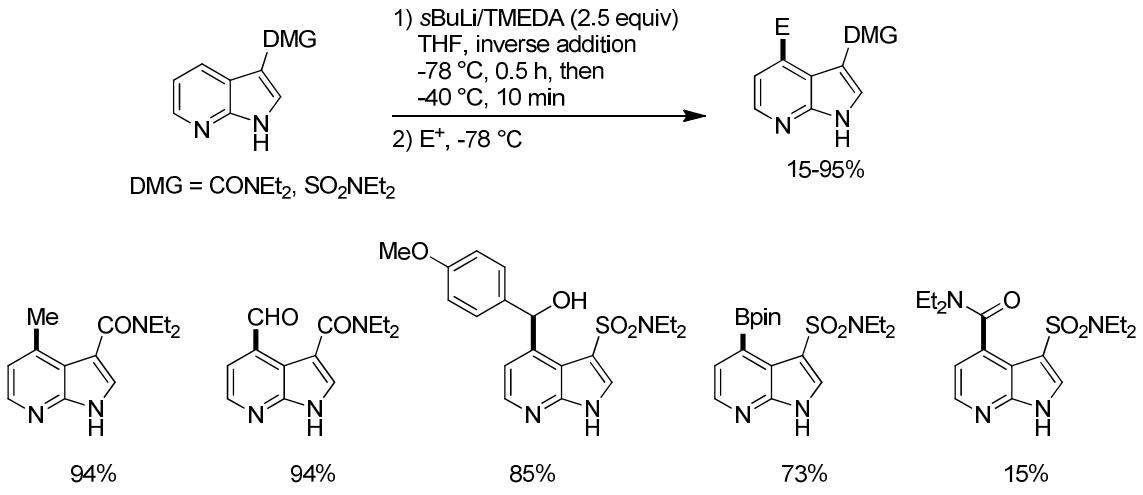
N1-Protection of the previously obtained 4-bromo compound (Scheme 38) with a TIPS-group (TIPS = tri*iso*propylsilyl) and subsequent Br/Li exchange using *t*BuLi[119] produced the fluoro azaindole after reaction with *N*-fluorobenzenesulfinimide (NFSI) (Scheme 40).[116] Noteworthy, this derivative displays a useful substrate for further functionalizations in position 5, which will be discussed in the next chapter (4.3.3). Also without previous N1-protection, the bromo derivative was subjected to a Br/Li exchange using MeLi and *t*BuLi to afford an alcohol (Scheme 40).[113] Furthermore, 4-bromo-7-azaindole displays a suitable electrophile for *Suzuki* cross-couplings affording the appropriate 4-arylated azaindole in quantitative yield (Scheme 40).[120]

[117] J. Guillard, M. Decrop, N. Gallay, C. Espanel, E. Boissier, O. Herault, M.-C. Viaud-Massuard, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1934.
[118] X. Wang, B. Zhi, J. Baum, Y. Chen, R. Crockett, L. Huang, S. Eisenberg, J. Ng, R. Larsen, M. Martinelli, P. Reider, *J. Org. Chem.* **2006**, *71*, 4021.
[119] P. D. Bartlett, C. Gardner Swain, R. B. Woodward, *J. Am. Chem. Soc.***1941**, *63*, 3229.
[120] T. Wang, J. P. Duffy, J. Wang, S. Halas, F. G. Salituro, A. C. Pierce, H. J. Zuccola, J. R. Black, J. K. Hogan, S. Jepson, D. Shlyakter, S. Mahajan, Y. Gu, T. Hoock, M. Wood, B. F. Furey, J. D. Frantz, L. M. Dauffenbach, U. A. Germann, B. Fan, M. Namchuk, Y. L. Bennani, M. W. Ledeboer, *J. Med. Chem.* **2009**, *52*, 7938.



Scheme 40: C4-functionalization starting from 4-bromo-7-azaindole.

In 2012, *Snieckus* elegantly demonstrated *peri*(C4)-lithiation of 3-amido and 3-sulfonamido 7-azaindoles for the synthesis of various 3,4-disubstituted 7-azaindoles.[121] Thereby, the appropriate amido- and sulfonamido-groups at C3 served as directed metalation group (DMG) to enable directed *ortho*-metalation (D*o*M)[29] using a mixture of *s*BuLi[122] and *N*,*N*,*N*',*N*'-tetramethylethane-1,2-diamine (TMEDA). Remarkably, metalation occured regioselectively in position 4 instead of C2 due to the unprotected amine function of the 7-azaindole which leads to an anionic shielding effect (Scheme **41**).

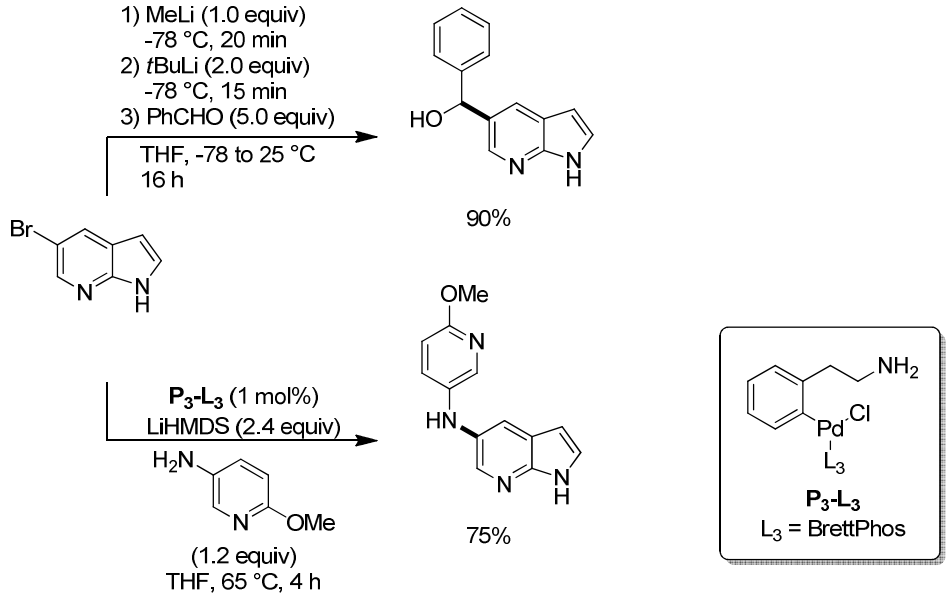


Scheme 41: C4-functionalization starting from 3-substituted azaindoles *via peri*(C4)-metalation.

[121] C. Schneider, E. David, A. A. Toutov, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 2722.
[122] H. Gilman, F. W. Moore, O. Baine, *J. Am. Chem. Soc.* **1941**, *63*, 2479.

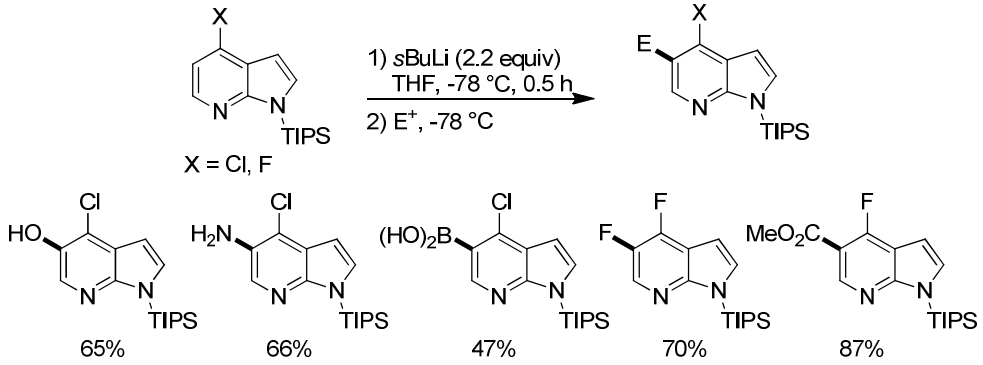
4.3.3 FUNCTIONALIZATION OF POSITION 5 OF THE 7-AZAINDOLE SCAFFOLD

So far, the functionalization of position 5 in the 7-azaindole skeleton has not been straightforward and only a few procedures are known. In this context, 5-brominated 7-azaindole displays a useful precursor and may serve either as nucleophile or electrophile in subsequent organometallic protocols. Thus, Br/Li exchange using MeLi and *t*BuLi[119] and reaction with benzaldehyde afforded the appropriate alcohol.[113] Furthermore, 5-bromo-7-azaindole was smoothly converted to an amine by Pd-catalyzed amination using the catalytic system P_3-L_3 (P_3 = precatalyst; L_3 = BrettPhos; Scheme 42).[123]



Scheme 42: C5-functionalization starting from 5-bromo-7-azaindole.

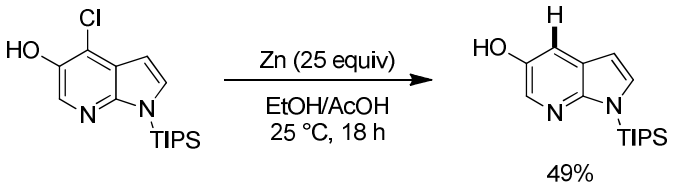
Also, previously mentioned 4-fluoro (Scheme 39) and 4-chloro-7-azaindoles (Scheme 40) gave way to C5-functionalization by means of directed *ortho*-metalation[29] (Scheme 43).[124]



Scheme 43: C5-functionalization from 4-halo azaindoles *via* directed *ortho*-metalation.

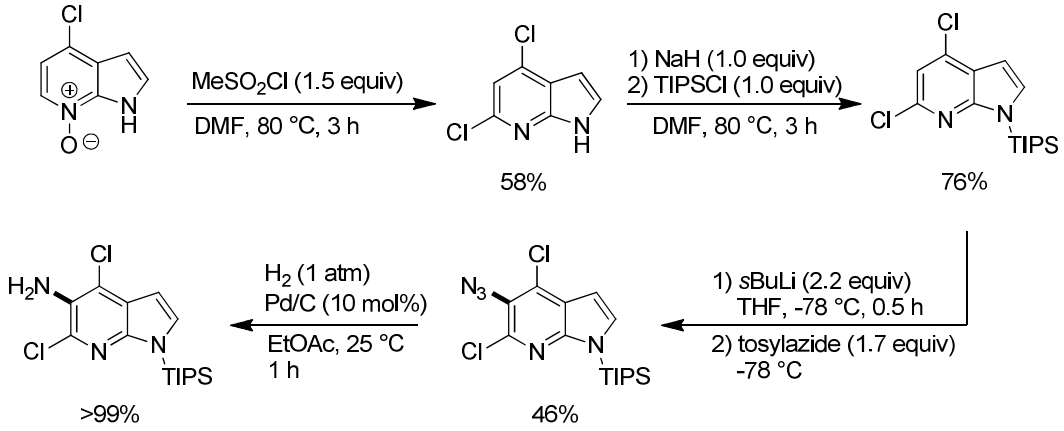
[123] J. L. Henderson, S. M. McDermott, S. L. Buchwald, *Org. Lett.* **2010**, *12*, 4438.
[124] A. L'Heureux, C. Thibault, R. Ruel, *Tetrahedron Lett.* **2004**, 2317.

To this end, *L'Heureux* and co-workers have described the directed *ortho*-lithiation using *s*BuLi[122] at -78 °C to afford the corresponding 4,5-disubstituted 7-azaindoles after reaction with electrophiles (Scheme 43).[124] Noteworthy, the chloride substitutent may be selectively removed in the presence of zinc in ethanol/acetic acid to produce a mono-functionalized 7-azaindole (Scheme 44).



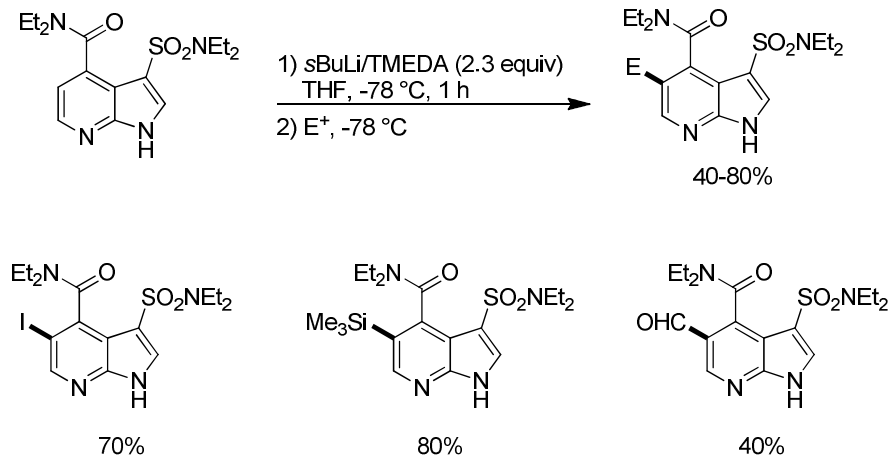
Scheme 44: Dechlorination using zinc.

Another approach for the C5-functionalization, also described by *L'Heureux et al.*, employed 4,6-dichloro-7-azaindole, readily obtained in 58% yield by chlorination of 4-chloro-7-azaindole-*N*-oxide using methanesulfonyl chloride. The thus-prepared azaindole was protected and subsequently treated with *s*BuLi to give an azide after reaction with tosylazide. Reduction to the amine afforded the 4,5-6-trisubstituted 7-azaindole quantitatively (Scheme 45).



Scheme 45: C5-functionalization from a dichlorinated azaindole *via* metalation.

The aforementioned method for the regioselective *peri*(C4)-metalation of the 7-azaindole skeleton reported by *Snieckus et al.* also proved to afford useful precursors for a subsequent substitution in position 5.[121] Thus, when 3,4-substituted azaindole was treated with *s*BuLi/TMEDA (2.3 equiv), subsequent trapping with electrophiles furnished 3,4,5-trisubstituted azaindoles in good yields (Scheme 46).

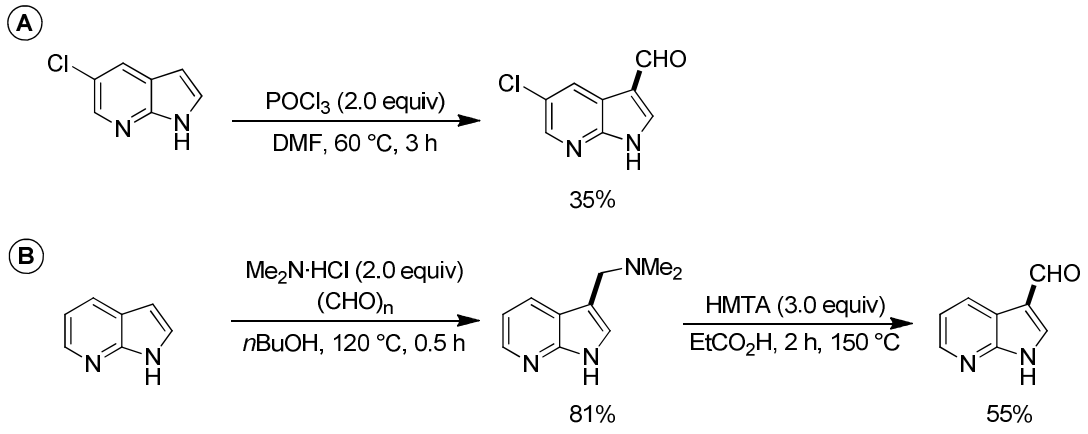


Scheme 46: C5-functionalization from an amido azaindole *via* directed *ortho*-metalation.

4.3.4 Functionalization of Position 3 of the 7-Azaindole Scaffold

Compared to indole, the relative nucleophilicity of 7-azaindole is decreased, probably due to the electron-deficient pyridine ring. This fact leads to a kind of inertness of the C3-position when it comes to reactions with electrophiles.[73a] Hence, it was tried to overcome these problems by either functionalizing the C3-position simultaneously with the construction of the 7-azaindole core, by increasing the nucleophilicity of the azaindole or by activating the electrophile towards nucleophilic attack.

Classical *Vilsmeier-Haack* formylation reactions proved to be difficult when applied to the 7-azaindole core and often resulted in only modest yields. Hence, the reaction of 5-bromo-7-azaindole with $POCl_3$ in DMF afforded the 3-formylated heterocycle in only 35% yield (Scheme 47; **A**).[125]

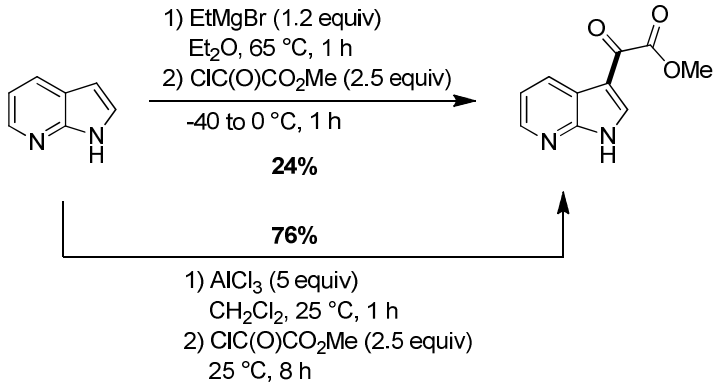


Scheme 47: C3-formylation of azaindoles.

[125] R. Nirogi, A. Shinde, A. Daulatabad, R. Kambhampati, P. Gudla, M. Shaik, M. Gampa, S. Balasubramaniam, P. Gangadasari, V. Reballi, R. Badange, K. Bojja, R. Subramanian, G. Bhyrapuneni, N. Muddana, P. Jayarajan, *J. Med. Chem.* **2012**, *55*, 9255.

Noteworthy, such formyl groups may as well be introduced in an indirect pathway. Already in 1955, *Robison et al.* described the *Mannich* reaction of 7-azaindole to afford an aza-gramine derivative in 81% yield which was reacted with hexamethylenetetramine (HMTA) in acidic media to furnish the 3-formyl-7-azaindole in 55% yield (Scheme 47; **B**).[126]

Especially acylation reactions in the 3-position of azaindoles remain challenging due to the decreased nucleophilic character of azaindoles. For example, while there are numerous literature procedures for the reaction of indoles with oxalyl chloride (mostly in Et_2O at 0 °C, 1 h) providing the 3-acylated indoles in >90% yield,[127] reported examples for the corresponding reaction of 7-azaindoles with oxalyl chloride are rather scarce.[128] As mentioned before, the outcome of such reactions may be improved either by enhancement of the nucleophilicity of the 7-azaindole or by activation of the electrophile. One example for upgrading the nucleophilicity of the azaindole is described in the reaction of 7-azaindole with EtMgBr to furnish a magnesium intermediate which was further reacted with methyl 2-chloro-2-oxoacetate to give the appropriate ester in a moderate yield of 24% (Scheme 48).[129]



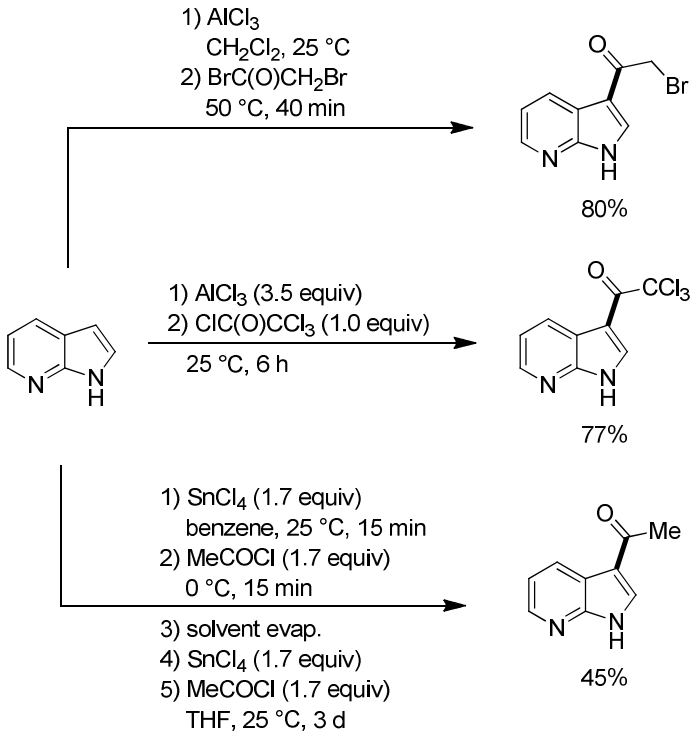
Scheme 48: C3-acylation of 7-azaindole.

In contrast, *Wang* reported the synthesis of this ester in 76% yield by the use of $AlCl_3$ in a *Friedel-Crafts*-type acylation of 7-azaindole with methyl 2-chloro-2-oxoacetate and thus, showed a successful example for the activation of electrophiles (Scheme 48).[130] Noteworthy, a minimum of 3 equivalents of $AlCl_3$ was required, since 2 equivalents are

[126] M. M. Robison, B. L. Robison, *J. Am. Chem. Soc.* **1955**, *77*, 457.
[127] For an example for the reaction of indole and oxalyl chloride, see: X. Guinchard, Y. Vallée, J.-N. Denis, *J. Org. Chem.* **2007**, *9*, 3761.
[128] T. Wang, O. B. Wallace, Z. Zhongzing, N. A. Meanwell, J. A. Bender, US 2011/0119982, **2002**.
[129] H.-C. Zhang, G.-H. Kuo, B. E. Maryanoff, H. Ye, D. O'Neill, L. Shen, K. Demarest, B. Conway, D. F. McComsey, WO 03/095452, **2003**.
[130] Z. Zhang, Z. Yang, H. Wong, J. Zhu, N. A. Meanwell, J. F. Kadow, T. Wang, *J. Org. Chem.* **2002**, *67*, 6226.

coordinated by the N1- and the N7-atom of the 7-azaindole core and thus, the third equivalent is necessary to form the active ate-complex with the acyl chloride.[130]

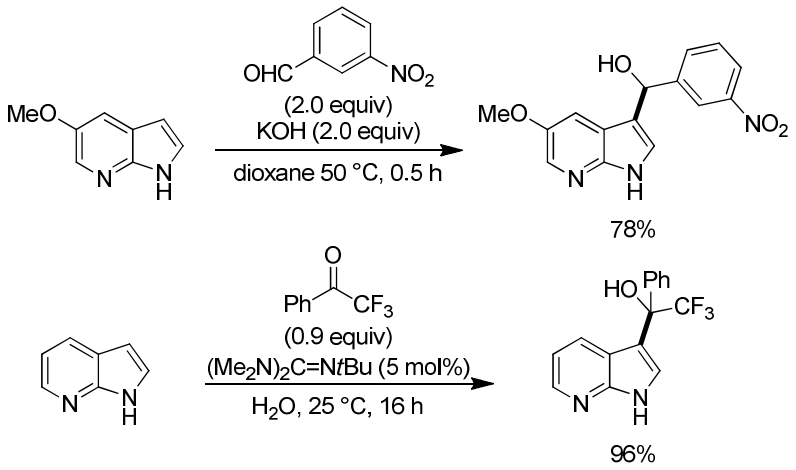
In comparison to the first approach enhancing the nucleophilic power of 7-azaindole, activation of the electrophile using Lewis Acids such as $AlCl_3$ proved to be a more suitable strategy for guaranteeing proper acylation reactions in the C3-position, which was successfully applied to the synthesis of other 3-acylated heterocycles (Scheme 49).[131,132] Instead of $AlCl_3$, also the Lewis Acid $SnCl_4$ could be applied for the *Friedel-Crafts* acylation of 7-azaindole (Scheme 49).[133]



Scheme 49: Further C3-acylation reactions of 7-azaindole.

Despite the low nucleophilicity of the 7-azaindole skeleton, there are some literature reports describing the reaction of N1-unprotected 7-azaindoles with aldehydes and ketones producing the corresponding 3-substituted derivatives in good yields (Scheme 50).[134,135]

[131] P. Diana, A. Carbone, P. Barraja, A. Montalbano, B. Parrino, A. Lopergolo, A. Pennati, N. Zaffaroni, G. Cirrincione, *ChemMedChem* **2011**, *6*, 1300.
[132] K. E. Lind (Sunsesis Pharmaceuticals; Biogen Idec Inc.), WO 2008/005457, **2008**.
[133] P. M. Fresneda, P. Molina, J. A. Bleda, *Tetrahedron* **2001**, *57*, 2355.
[134] G. C. Visor, P. N. Ibrahim, W. Spevak, H. Cho, S. Shi, G. Wu, WO 2010/129570, **2010**.
[135] M. Bandini, R. Sinisi, *Org. Lett.* **2009**, *11*, 2093.

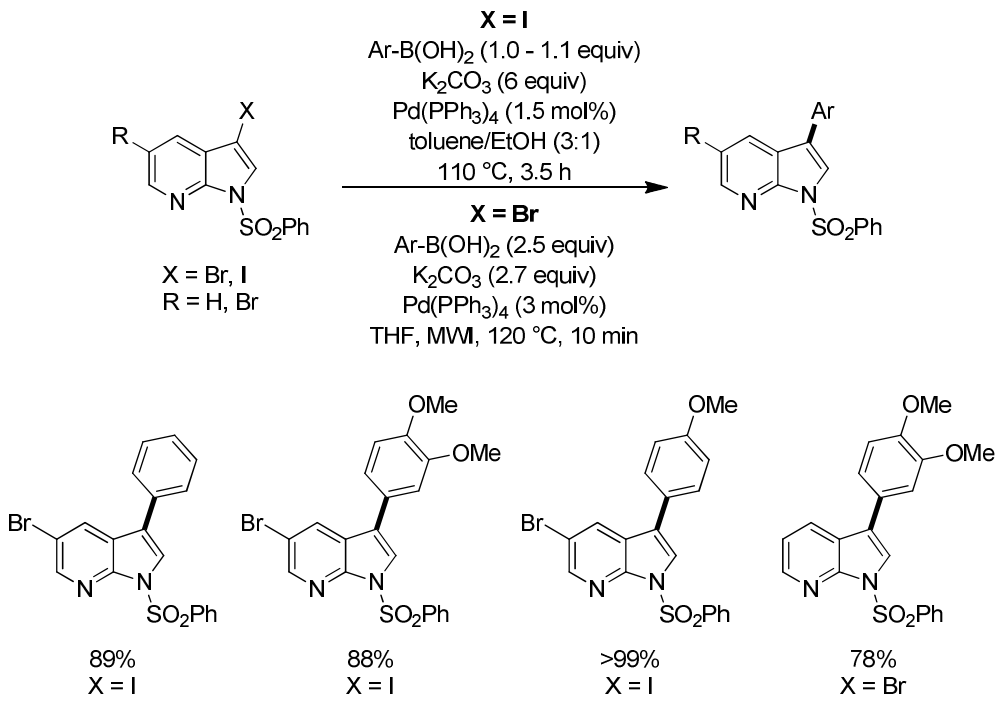


Scheme 50: C3-functionalization of azaindoles *via* reaction with aldehydes and ketones.

One of the most important reactions for the C3-functionalization of 7-azaindoles probably consists in the halogenation affording various brominated and iodinated azaindoles. Thereby, common strategies for the bromination of these heterocycles mostly involve neat bromine in solvents such as $CHCl_3$[136] and DMF[137] and *N*-bromosuccinimide (NBS) in $CHCl_3$,[138] THF[139] and DMF.[132] C3-iodination is usually achieved by reaction of these heterocycles with KOH and I_2,[121] *N*-iodosuccinimide (NIS)[140] or ICl.[141]

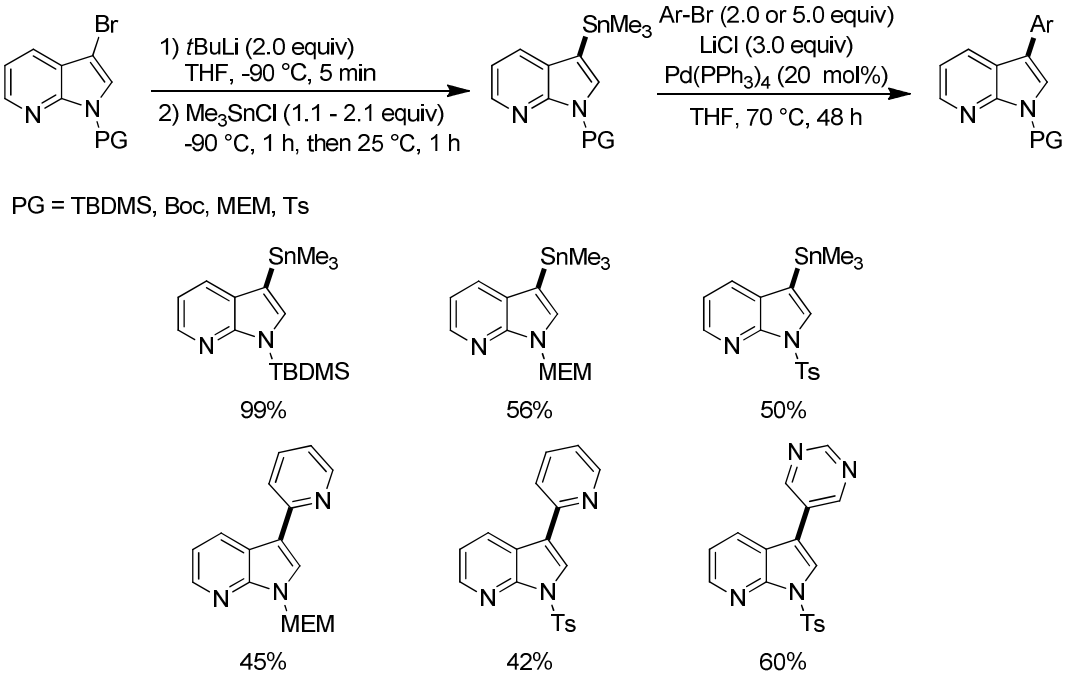
The thus-prepared halogenated substrates may then serve as electrophiles in, for example, *Suzuki* cross-couplings with various boronic acids giving access to a variety of 3-functionalized azaindoles (Scheme 51).[142,143]

[136] F. Salituro (Vertex Pharmaceuticals Incorporated), WO 2005/095400, **2005**.
[137] G. J. Tanoury (Vertex Pharmaceuticals Incorporated), WO 2013/006634, **2013**.
[138] S. Bahceci (Exelixis Inc.), WO 210/003133, **2010**.
[139] A. Florjancic, Y. Tong, T. Penning, WO 2011/008915, **2011**.
[140] T. Ishiyama (Nippon Steel Chemical Co., Ltd.), WO 2012/124412, **2012**.
[141] S. Hamri, J. Rodríguez, J. Basset, G. Guillaumet, M. D. Pujol, *Tetrahedron* **2012**, *68*, 6269.
[142] S. Gourdain, J. Dairou, C. Denhez, L. C. Bui, F. Rodrigues-Lima, N. Janel, J. M. Delabar, K. Cariou, R. H. Dodd, *J. Med. Chem.* **2013**, *56*, 9569.
[143] P. A. Harris, D. Bandyopadhyay, S. B. Berger, N. Campobasso, C. A. Capriotti, J. A. Cox, L. Dare, J. N. Funger, S. J. Hoffman, K. M. Kahler, R. Lehr, J. D. Lich, R. Nagilla, R. T. Nolte, M. T. Ouellette, C. S. Pao, M. C. Schaeffer, A. Smallwood, H. H. Sun, B. A. Swift, D. Totoritis, P. Ward, R. W. Marquis, J. Bertin, P. J. Gough, *ACS Med. Chem. Lett.* **2013**, *4*, 1238.



Scheme 51: C3-functionalization of 3-halogenated azaindoles *via Suzuki* cross-coupling.

Noteworthy, these halogenated compounds may as well be employed in a halogen/lithium exchange using *t*BuLi to produce stannane derivatives, which display valuable nucelophiles in subsequent Pd-catalyzed *Stille* cross-coupling reactions to produce the corresponding 3-substituted azaindoles (Scheme 52).[144]

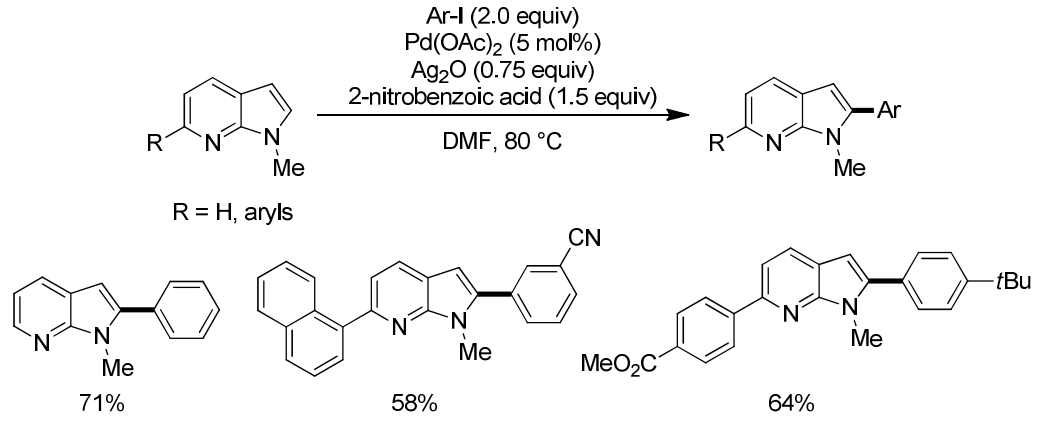


Scheme 52: C3-functionalization of azaindoles *via* Br/Li exchange and *Suzuki* cross-coupling; TBDMS = *tert*-butyldimethylsilyl, MEM = methoxyethoxymethyl ether.

[144] M. Alvarez, D. Fernández, J. A. Joule, *Synthesis* **1999**, 615.

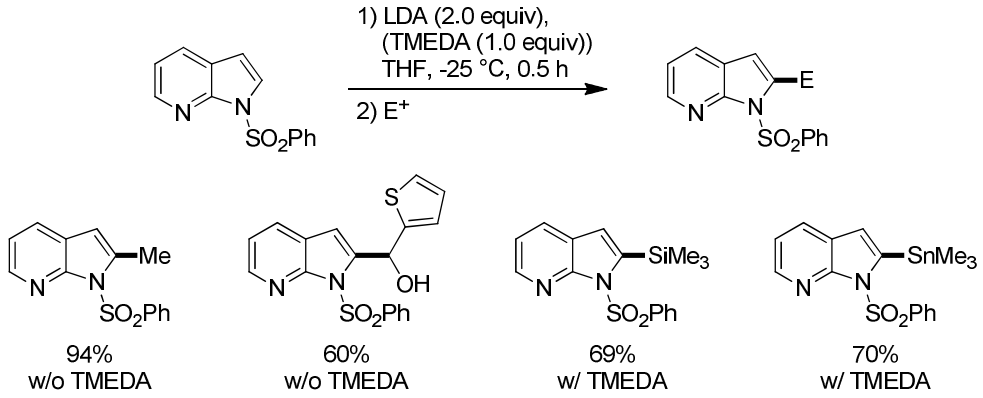
4.3.5 FUNCTIONALIZATION OF POSITION 2 OF THE 7-AZAINDOLE SCAFFOLD

C2-functionalization of 7-azaindole compounds was achieved mostly through organometallic strategies. For example, C2-arylation of azaindoles with phenyliodides in the presence of $Pd(OAc)_2$ and Ag_2O furnishes the functionalized heterocycles in good yields (Scheme 53).[145]



Scheme 53: C2-functionalization of azaindoles *via* direct arylation.

Lithiations of N1-protected azaindoles using lithium bases such as *n*BuLi,[108] LDA[105] or TMPLi[146] display the most convenient approach to C2-substituted 7-azaindoles. *Mérour* and co-workers have described the *ortho*-lithiation[29] of protected 7-azaindoles with LDA in the presence or absence of TMEDA to obtain various 2-substituted azaindoles after reaction with electrophiles (Scheme 54).[147]

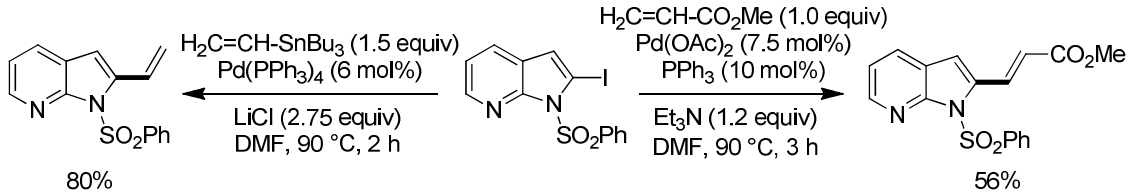


Scheme 54: C2-functionalization of azaindoles *via ortho*-lithiation.

Noteworthy, the aforementioned lithiation strategy also gives access to 2-halogenated 7-azaindoles which proved to be suitable electrophiles for cross-coupling reactions.

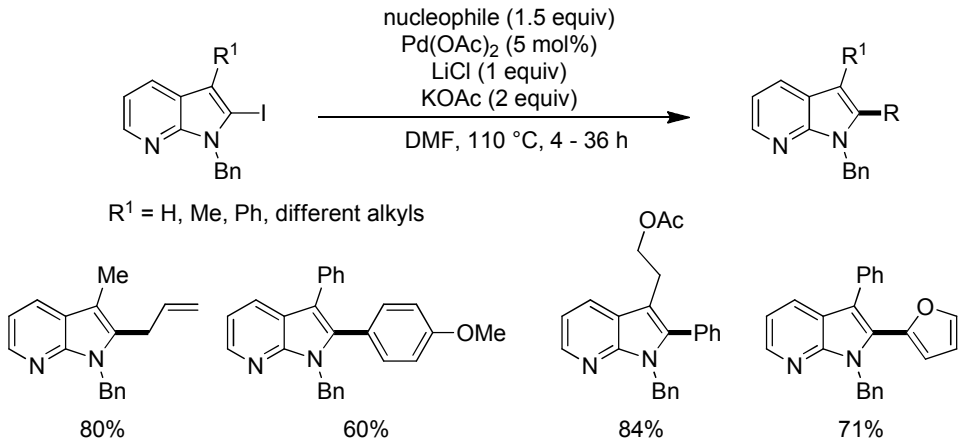
[145] M. P. Huestis, K. Fagnou, *Org. Lett.* **2009**, *11*, 1357.
[146] a) C. L. Kissel, B. Rickborn, *J. Org. Chem*, **1972**, *37*, 2060. b) M. W. Rathke, R. Kow, *J. Am. Chem. Soc.* **1972**, *94*, 6854.
[147] E. Desarbre, S. Coudret, C. Meheust, J.-Y. Mérour, *Tetrahedron* **1997**, *53*, 3637.

Hence, in 2000, *Mérour et al.* disclosed the synthesis of 2-vinyl-7-azaindoles by Pd-cross-couplings of $PhSO_2$-protected 2-iodo-7-azaindoles with vinyltributyltin (*Stille*[92] coupling) and methyl acrylate (*Heck*[88] coupling) to furnish the appropriate 2-functionalized heterocycles (Scheme 55).[148]



Scheme 55: C2-functionalization of an iodo azaindole *via Stille* and *Heck* cross-couplings.

Similarly, *Yum* and coworkers reported the preparation of 2,3-substituted 7-azaindoles *via* Pd-catalyzed *Stille*, *Suzuki*[90] and *Heck* cross-coupling reactions of 2-iodo-3-functionalized compounds with different nucleophiles (Scheme 56).[149]

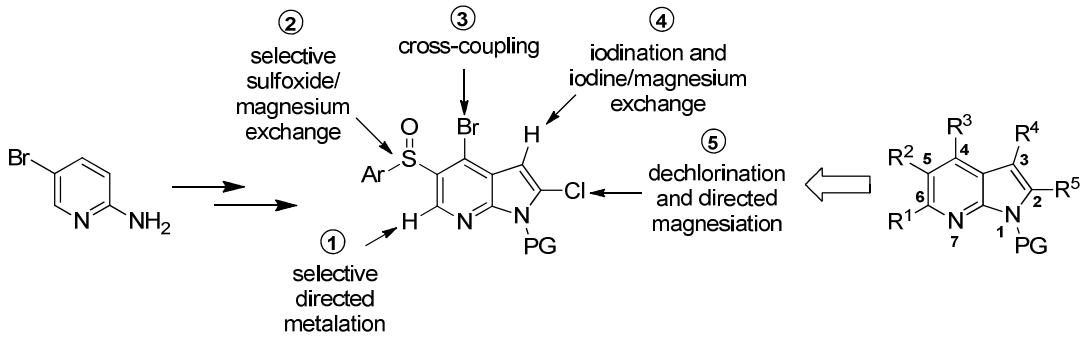


Scheme 56: C2-functionalization of iodo azaindoles *via Stille*, *Suzuki* and *Heck* cross-couplings.

[148] B. Joseph, H. Da Costa, J.-Y. Mérour, S. Léonce, *Tetrahedron* **2000**, *56*, 3189.
[149] S. M. Chi, J.-K. Choi, E. K. Yum, D. Y. Chi, *Tetrahedron Lett.* **2000**, *41*, 919.

5. OBJECTIVES

7-Azaindoles represent an essential class of *N*-heterocycles which is drawing more and more attention with respect to the development of materials, agrochemicals and especially new potent therapeutic agents, making an easy approach to highly functionalized azaindoles indispensible. However, to date, the majority of synthetic strategies involving the functionalization of 7-azaindoles give access to N1-, C2- and C3-substituted derivatives, while there are only few approaches reported offering the general functionalization of positions 4, 5 and 6. This fact underlines the challenges both synthetic and *e.g.* medicinal chemists have to face in their search for properly functionalized 7-azaindole derivatives displaying potent therapeutics. Thus, we envisioned the development of a convenient and general method for the regioselective and stepwise full-functionalization of the 7-azaindole scaffold starting from commercially available 2-amino-5-bromopyridine. To this end, an appropriately substituted azaindole precursor should be prepared which allows the functionalization of all five carbon positions of the 7-azaindole skeleton in a predictable manner (Scheme 57).[150]

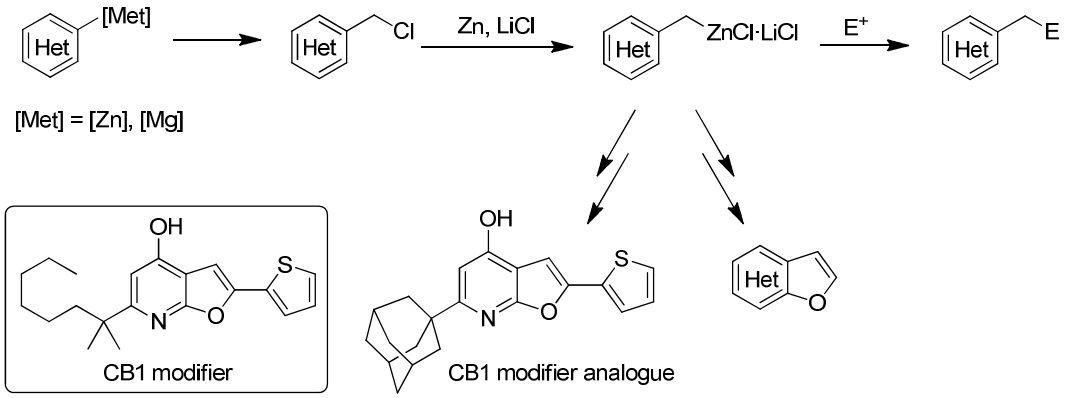


Scheme 57: Full-Functionalization of the 7-azaindole scaffold starting from 2-amino-5-bromopyridine; Ar = 4-methoxy-3,5-dimethyl-phenyl; PG = protective group.

Organozinc derivatives have found broad applications in organic synthesis and are of key importance for the functionalization of *e.g.* heteroarenes. In this context, a main aim of this work was the general and convenient preparation of heteroarylmethylzinc reagents by direct LiCl-promoted zinc insertion into the corresponding chloromethyl heteroarenes. Thereby, the focus lay also on the development of a facile synthesis for these chloromethyl precursors, which should be readily available from the appropriate heteroaryl organometallics. Furthermore, the prepared zinc reagents should be employed

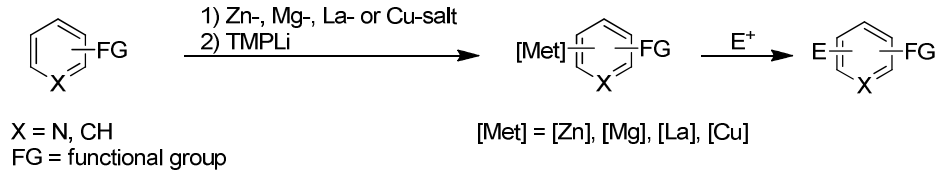
[150] This project was developed in cooperation with E. Sansiaume-Dagousset.

in ring closing reactions to furnish a variety of annulated heterocycles which, among others, should also give access to an analogue of a reported CB1 modifier (Scheme 58).[151]



Scheme 58: Preparation of chloromethyl heterocycles, their conversion to zinc reagents, subsequent reactions with electrophiles and synthesis of annulated heterocycles.

The direct metalation of (hetero)arenes displays an efficient tool in organic synthesis. Hence, in the last part of this work, a new method for the metalation of sensitive functionalized aromatics and heteroarenes should be developed, employing the use of the strong amide base TMPLi in the presence of metal salts such as $ZnCl_2$, $MgCl_2$, CuCN and $LaCl_3$ (*in situ* trapping method) to generate viable Zn-, Mg-, Cu- and La-intermediates readily reacting with various electrophiles (Scheme **59**).[152]



Scheme 59: Metalation of (hetero)arenes using TMPLi in the presence of Zn-, Mg-, Cu- and La-salts, and subsequent functionalization with electrophiles.

[151] This project was developed in cooperation with A. J. Wagner (see Ph.D. thesis Andreas Johannes Wagner, LMU Munich, **2011**), G. A. Monzón Díaz (see: Ph.D. thesis Gabriel Andrés Monzón Díaz, LMU Munich, **2012**) and E. Sansiaume-Dagousset.

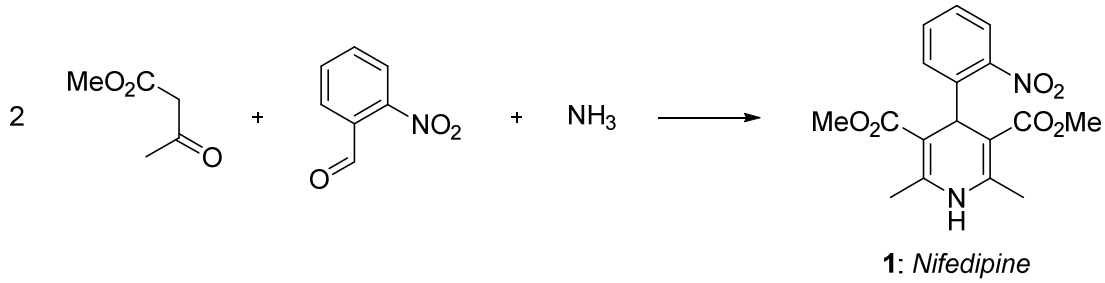
[152] This project was developed in cooperation with A. Frischmuth (see Ph.D. thesis Annette Frischmuth, LMU Munich, **2014**) and M. Fernández.

B. Results and Discussion

1. SYNTHESIS AND FULL-FUNCTIONALIZATION OF THE 7-AZAINDOLE SCAFFOLD *VIA* SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

1.1 INTRODUCTION

Nowadays, polysubstituted heteroarenes play a very important economic role, since they find applications in biology, dye industry, agrochemistry, material science and especially in pharmaceutics.[153] As a consequence, a general, convenient and adaptable approach for designing and functionalizing such heterocyclic scaffolds is highly desirable. In general, polysubstituted heterocycles are mainly accessible *via* two pathways. The first method involves the construction of the heterocyclic core after certain substituents have already been chosen and pre-installed. Exemplary for this route is the synthesis of *Nifedipine*[154] (**1**; contained in the pharmaceutic *Adalate*®) by a symmetric *Hantzsch* pyridine synthesis (Scheme 60).



Scheme 60: Symmetrical *Hantzsch* pyridine synthesis of *Nifedipine*.

The necessity to install certain substituents prior to the construction of the heterocycle results in a drastic limitation referring to the scope of available functionalities, since sensitive moieties have to be taken into consideration with regard to the reaction conditions used for the subsequent assembly of the heterocycle. Moreover, this route

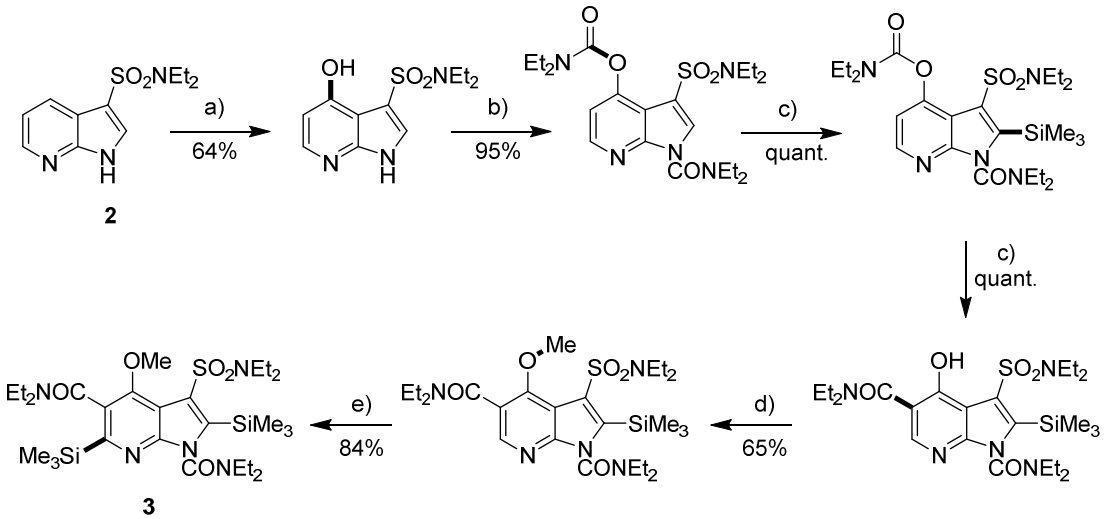
[153] a) *Heterocylic Chemistry* (Ed.: T. L. Gilchrist), Longman, London, **1998**. b) J. F. Miller, A. Termin, K. Koch, A. D. Piscopio, *J. Org. Chem.* **1998**, *63*, 3158. c) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449. d) *Organolithiums: Selectivity for Synthesis. Tetrahedron Organic Chemistry Series* (Ed.: J. Clayden), Pergamon, Oxford, **2002**. e) H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Comm.* **2006**, 583. f) K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman, A. J. Souers, *Org. Lett.* **2003**, *5*, 2131. g) J. P. Wolfe, J. S. Thomas, *Curr. Org. Chem.* **2005**, *9*, 625. h) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. i) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036. j) C. Schmuck, D. Rupprecht, *Synthesis* **2007**, 3095. k) S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158. l) R. Ponce Ortiz, J. Casado, V. Hernández, J. T. López Navarrete, J. A. Letizia, M. A. Ratner, A. Facchetti, T. J. Marks, *Chem. Eur. J.* **2009**, *15*, 5023. m) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874. n) F. M. Piller, P. Knochel, *Org. Lett.* **2009**, *11*, 445. o) P. Thansandote, C. Gouliaras, M.-O. Turcotte-Savard, M. Lautens, *J. Org. Chem.* **2009**, *74*, 1791. p) C. J. O'Connor, M. D. Roydhouse, A. M. Przybył, M. D. Wall, J. M. Southern, *J. Org. Chem.* **2010**, *75*, 2534. q) M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8520. r) F. Miege, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2011**, *50*, 5932. s) S. Benetti, C. De Risi, G. P. Pollini, V. Zanirato, *Chem. Rev.* **2012**, *112*, 2129. t) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nature Chem.* **2012**, *4*, 130.

[154] D. Steinhoff, E. Grundmann, *Naturwissenschaften* **1971**, *58*, 578.

might turn out to be quite tedious when modifying the heterocyclic core, as some steps have to be repeated with varying starting materials.

In contrast, the second synthetic pathway to highly functionalized heterocycles refers to the successive introduction of certain functionalities after the heterocyclic scaffold has already been constructed. Thus, a higher generality is guaranteed regarding the introduction of functional groups, and modification of the heterocycle is less complicated. Thereby, organometallic methods such as cross-coupling reactions, direct metalation and halogen/metal exchange proved to be quite suitable, and the full-functionalization of the pyridine[155] and the purine scaffold,[156] for example, has successfully been realized.

Due to their interesting cytotoxical properties, especially 7-azaindoles have attracted lots of attention when it comes to the development of new therapeutic agents.[73-76] Also here, a general and mild approach to poly- or even fully substituted 7-azaindole derivatives would be highly advantageous, but has proven to be quite difficult up to now.[73] Recently, *Snieckus* described an elegant ring-walk metalation of the 7-azaindole scaffold starting from **2** by iterative lithiation furnishing the fully dressed azaindole derivative **3** (Scheme 61).[121]



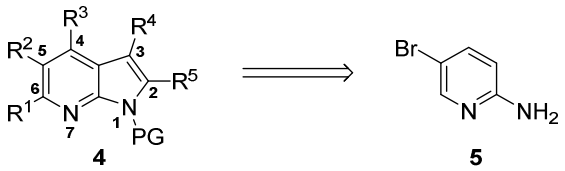
Scheme 61: Ring-walk metalation sequence to **3**. a) DIPEA (2.4 equiv), $ClCONEt_2$ (3.0 equiv), py, 25 °C; b) TMPLi (1.2 equiv), TMSCl (1.2 equiv), THF, -78 °C, 1 h; c) sBuLi/TMEDA (1.3 equiv), THF, -78 °C to 25 °C, 3 h; d) NaH (2.0 equiv), MeI (1.5 equiv), DMF, 25 °C, 12 h; e) TMPLi (2.5 equiv), TMSCl (3.0 equiv), THF, -78 °C, 1 h; DIPEA = diisopropylethylamine.

However, this method exclusively involves rather harsh lithium reagents such as *s*BuLi[122] and TMPLi.[146] Furthermore, all functionalizing steps are dependent on the

[155] M. Jaric, B. A Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306.
[156] S. Zimdars, X. Mollat Du Jourdin, F. Crestey, T. Carell, P. Knochel, *Org. Lett.* **2011**, *13*, 792.

previously installed, non-modifiable *ortho*-directing[29] $CONEt_2$- and SO_2NEt_2-groups, dramatically hampering the generality of this strategy.

In this context, we envisioned the development of a general, convenient, mild and efficient strategy for the regioselective full-functionalization of the 7-azaindole scaffold allowing the substitution of all five carbon positions of the azaindole core in a predictable manner to furnish fully substituted azaindole derivatives of type **4**. Thus, for achieving this synthetic goal, an appropriately substituted 7-azaindole precursor should be prepared starting from commercially available 2-amino-5-bromopyridine (**5**; Scheme 62).

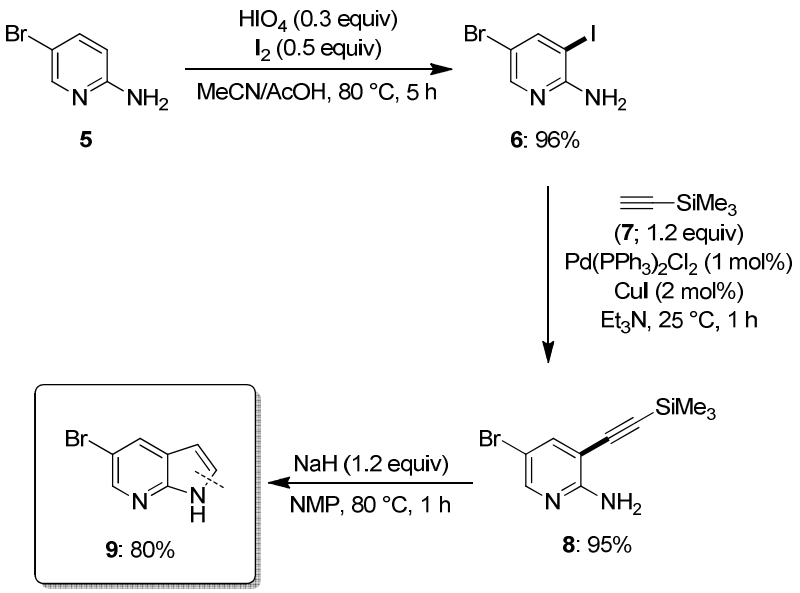


Scheme 62: Full Functionalization of the 7-azaindole scaffold starting from 2-amino-5-bromopyridine **5** affording fully substituted azaindoles derivatives of type **4**.

1.2 SYNTHESIS OF THE 7-AZAINDOLE RING

First, the 7-azaindole backbone had to be prepared starting from 2-amino-5-bromopyridine (**5**). In this context, we chose to build the azaindole core by Pd-catalyzed cross-coupling of an *ortho*-aminoiodopyridine with an internal alkyne, as described before (see A, Chapter 4.2.1). Thus, **5** was iodinated (HIO_4, I_2) regioselectively at C3 in a mixture of acetonitrile and acetic acid[157] (80 °C, 5 h) to furnish the 3-iodopyridine **6** in 96% yield. Subsequent *Sonogashira* cross-coupling[96] of **6** in triethylamine (Et_3N) using trimethylsilylacetylene (**7**) in the presence of $Pd(PPh_3)_2Cl_2$ (1 mol%) and CuI[158] (2 mol%, 25 °C, 1 h) gave the aminopyridine **8** in 95% yield. For the construction of the 7-azaindole core, a thermal ring closure was conducted by addition of NaH (1.2 equiv) in NMP (80 °C, 1 h),[100] which led to the desired 7-azaindole **9** in 80% yield (Scheme 63).

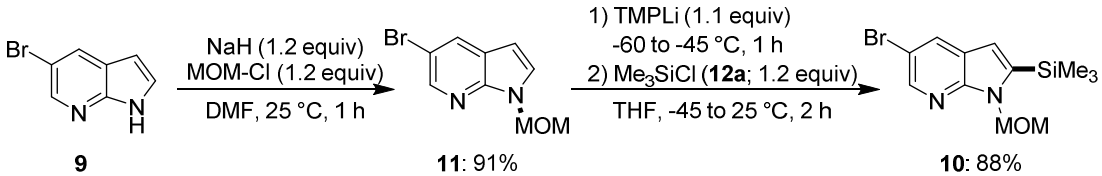
[157] S. Hildbrand, H.-J. Mair, R.-N. Radinov, Y. Ren, J. Anderson Wright, US 2011/0028511, **2011**.
[158] J. J. Cui (Pfizer Company), WO 2009/016460, **2009**.



Scheme 63: Preparation of the 7-azaindole **9** *via* selective iodination, *Sonogashira* cross-coupling and thermal ring closure.

1.3 First Attempts towards the Full-Functionalization of the 7-Azaindole Scaffold

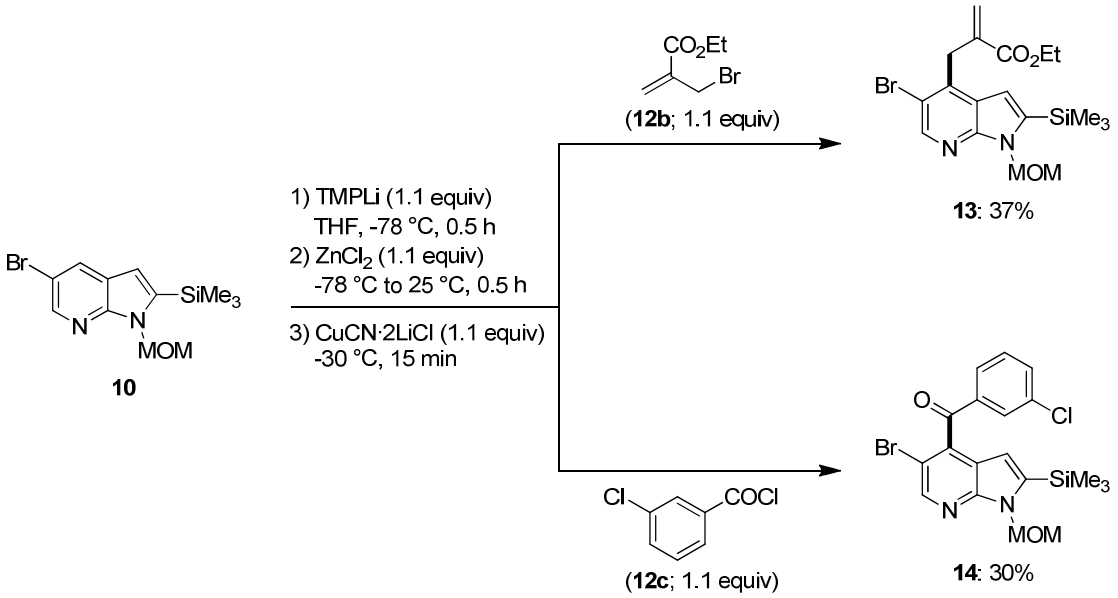
In our search for an appropriate 7-azaindole precursor allowing the general and stepwise full-functionalization of the azaindole scaffold, we decided to prepare the heterocyclic derivative **10**. Hence, the previously prepared 5-bromo-7-azaindole (**9**) was protected in the N1-position with a methoxymethyl (MOM) group (NaH, MOM-Cl, DMF, 25 °C, 1 h) to furnish **11** in 91% yield. The so-obtained 7-azaindole **11** was then selectively lithiated in position 2 using TMPLi[146] in THF (-60 °C to -45 °C, 1 h), and quenching with Me_3SiCl (**12a**) provided the silylated 7-azaindole **10** in 88% yield. This newly introduced silyl moiety serves as protecting group of position 2 and hampers a competitive metalation at C3 (Scheme 64).



Scheme 64: Protection of the 7-azaindole **9** in position N1 and C2.

With the substituted azaindole **10** in hand, we were aiming for the metalation of position 4 or 6 by direct metalation using TMP-derived bases. To this end, a variety of bases was investigated, however, only TMPLi (1.1 equiv, -78 °C, 0.5 h) gave acceptable results regarding the conversion of the starting material and the stability of the metalated

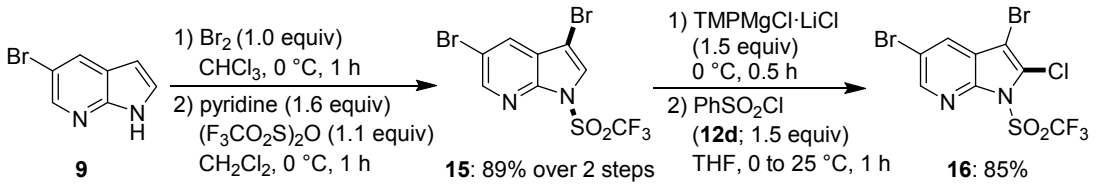
species, leading, after copper-mediated allylation with **12b**[159]and acylation with benzoyl chloride (**12c**),[160] to the corresponding 4-substituted products **13** and **14** in 30-37% yield (Scheme 65).[161]



Scheme 65: Metalation of the 7-azaindole **10** in position C4 using TMPLi, and subsequent functionalization.

Since already in the first step of the functionalization of the pyridyl-subunit, the rather strong base TMPLi had to be used, leading, nevertheless, to low yields for the allylation and acylation reactions, we decided to prepare another azaindole precursor. To this end, we envisioned to pre-instal mainly electron-withdrawing groups with the hope to increase the activity of the heterocyclic ring towards metalation to such extend that the use of milder bases such as TMPMgCl·LiCl[44] is possible. Hence, 5-bromo-7-azaindole (**9**) was regioselectively brominated and reacted with trifluoromethanesulfonic anhydride ($(F_3CO_2S)_2O$, 1.1 equiv) to give the N1-protected heteroarene **15** in 89% yield over 2 steps. Compared to the MOM-protecting group, this triflate-moiety shows an increased electron-withdrawing effect on the ring system and might be useful for subsequent metalations. Accordingly, metalative deprotonation of **15** could be accomplished using TMPMgCl·LiCl (1.5 equiv, 0 °C, 0.5 h) furnishing after chlorination with $PhSO_2Cl$[162] (**12d**) the 2-chlorinated azaindole **16** in 85% yield (Scheme 66).

[159] a) M. Rambaud, J. Villiéras, *Synthesis* **1984**, 406. b) J. Villiéras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.
[160] a) P. Knochel, M. Yeh, S. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390. b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.
[161] The regioselectivity of the metalation of the pyridyl part of the azaindole **10** using TMPLi is analogously to the one obtained upon treatment of 3-bromopyridine with LDA, see: G. W. Gribble, M. G. Saulnier, *Tetrahedron Lett.* **1980**, *21*, 4137.
[162] F. Chemla, I. Marek, J.-F. Normant, *Synlett* **1993**, 665.



Scheme 66: Preparation of the 7-azaindole **16** by bromination as well as N1-and C2-protection.

Then, we tested the newly prepared azaindole precursor **16** on its behavior upon metalation using the bases TMPZnCl·LiCl,[64] $TMP_2Zn·2MgCl·2LiCl$,[65] TMPMgCl·LiCl,[44] $TMP_2Mg·2LiCl$[45] and TMPLi.[146] For the two zinc bases, no reaction could be observed, even when the mixture was heated to 100 °C for 2 h under microwave irradiation. While not any metalation was obtained using a combination of TMPMgCl·LiCl and $BF_3·OEt_2$,[163] Mg-amide bases TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ mainly led to decomposition. To this end, we decided to metalate the azaindole derivative **16** under *Barbier* conditions[164,165] using TMPMgCl·LiCl, $TMP_2Mg·2LiCl$ and TMPLi by mixing the azaindole **16** with electrophiles such as methyl iodide and chlorotrimethylsilane and subsequently treating it with the appropriate base. None of these experiments delivered the desired products, but mentionable amounts of a regioisomer of **16** were formed as a consequence of "halogen dance".[166] Thus, an efficient metalation of the 7-azaindole **16** could not be accomplished.

We therefore thought of introducing the directing Me_2NCH_2-moiety[167] in the 3-position of the azaindole derivative **16**, since these amino groups are known to direct *peri*(C4)-metalation on naphthalenes[168] or azagramines[169] and thus, might help for an effective deprotonation of the azaindole core. Luckily, bromine/magnesium exchange using *i*PrMgCl·LiCl (1.1 equiv, -78 °C, 5 min) selectively proceeded in C3, and

[163] a) M. Jaric, B.A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451. b) S. M. Manolikakes, M. Jaric, K. Karaghiosoff, P. Knochel, *Chem. Commun.* **2013**, *49*, 2124. c) K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776. d) A. Unsinn, S. H. Wunderlich, A. Jana, K. Karaghiosoff, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 14687. e) T. Klatt, D. Sustac, T. Leon, P. Knochel, *Org. Lett.* **2014**, *16*, 1232.

[164] a) M. Lysén, J. L. Kristensen, P. Vedsø, M. Begtrup, *Org. Lett.* **2002**, *4*, 257. b) J. L. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435. c) H. M. Hansen, M. Begtrup, J. L. Kristensen, *J. Org. Chem.* **2006**, *71*, 2518.

[165] a) R. Chinchilla, C. Najera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667. b) F. D. Therkelsen, M. Rottländer, N. Thorup, E. Bjerregaard Pedersen, *Org. Lett.* **2004**, *6*, 1991.

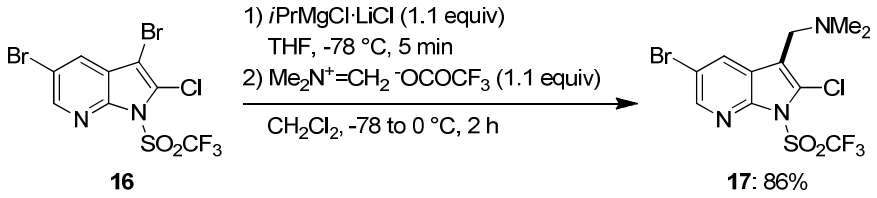
[166] a) P. Rocca, C. Cochonnec, F. Marsais, L. Thomas-dit-Dumont, A. Godard, G. Quéguiner, *J. Org. Chem.* **1993**, *58*, 7832. b) C. Cochonnec, P. Rocca, F. Marsais, A. Godard, G. Quéguiner, *Synthesis* **1995**, 321. c) F. Trécourt, B. Gervais, M. Mallet, G. Quéguiner, *J. Org. Chem.* **1996**, *61*, 1673.

[167] F. N. Jones, M. F. Zinn, C. R. Hauser, *J. Org. Chem.* **1963**, *28*, 663.

[168] R. L. Gay, C. R. Hauser, *J. Am. Chem. Soc.* **1967**, *89*, 2297. b) J. Clayden, C. S. Frampton, C. McCarthy, N. Westlund, *Tetrahedron* **1999**, *55*, 14161.

[169] P. Ibrahim, D. R. Artis, G. Habets, R. Zuckerman, US 2007/0066641, **2007**.

quenching with the *Mannich*'s salt methylene(dimethyl)iminium trifluoroacetate[170] gave the amino compound **17** in 86% yield (Scheme 67).



Scheme 67: Preparation of the 7-azaindole **17** by Br/Mg exchange.

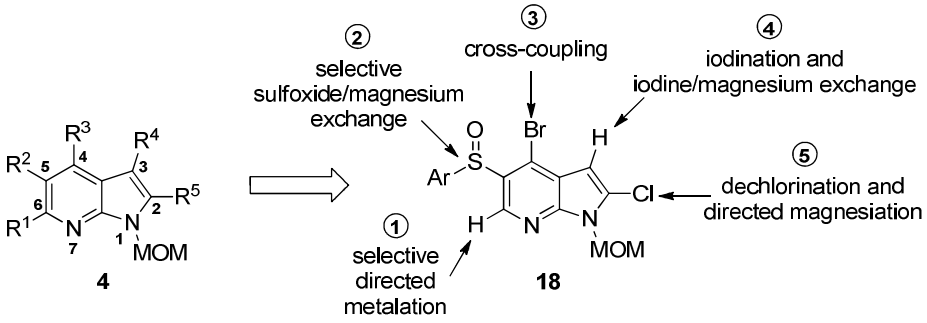
Having the thus-prepared amino-azaindole **17** in hand, we again investigated the deprotonative metalation of **17** with several bases. Treatment with TMPMgCl·LiCl led to decomposition and, again, the formation of a regioisomer of **17** due to halogen dance.[166] The same results were obtained using TMPMgCl·LiCl, TMPLi or LDA[105] under *Barbier* conditions[164,165] with chlorotrimethylsilane (**12a**) as electrophile. Thus, also the azaindole derivative **17** did not display a suitable precursor for an efficient and regioselective functionalization of the heterocyclic ring. As all of the preliminary results indicate, the pyridyl part of the 7-azaindole core is rather difficult to metalate in an effective manner and needs a stronger directing group. In addition, the triflate-protecting group turned out to be unsatisfactory. When **17** was subjected to a Br/Mg exchange on C3 followed by Cu-mediated acylation and allylation reactions,[160] loss of the N1-protection group was observed, indicating that the triflate-substitutent was not stable in the presence of the copper-salt and thus, precluding a general functionalization strategy.

Taking all these results into consideration, we made two choices. First, since there were no complications arising with the use of the aforementioned MOM-moiety as protective group, we again decided to introduce the MOM-group for N1-protection. Secondly, having the previously mentioned directing effect in mind, we envisioned the preparation of an azaindole precursor bearing a strong *ortho*-directing[29] substituent in position 5 activating the pyridyl-derived part of the azaindole scaffold towards metalation and alleviating functionalization of positions 4 and 6. Moreover, it would be highly desirable, if this *ortho*-directing group could be further modified offering the opportunity to successively and regioselectively substitute all five carbon positions of the azaindole core in a predictable manner.

[170] For more details on the preparation and the use of this reagent, please refer to: B. Results and Discussion, Chapter 2.

1.4 SYNTHESIS OF THE KEY 7-AZAINDOLE PRECURSOR

Thus, for achieving the synthesis of fully substituted 7-azaindoles of type **4**, we prepared the azaindole derivative **18** which allowed us to use a combination of directed magnesiations and lithiations,[171] halogen/magnesium[32] and sulfoxide/magnesium exchange[33,34,38,40] (Scheme 68).



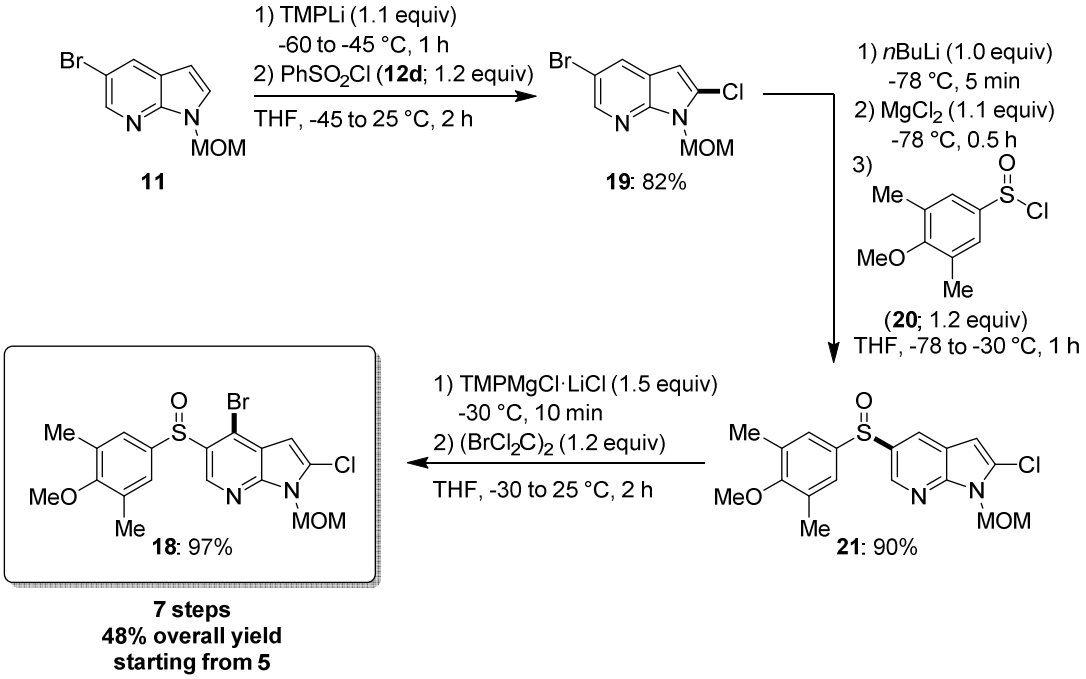
Scheme 68: Key 7-azaindole scaffold **18** allowing the preparation of fully substituted 7-azaindoles of type **4**; Ar = 4-methoxy-3,5-dimethyl-phenyl.

In this context, we employed a sulfoxide group on position C5 which turned out to be crucial for the entire full functionalization protocol. On the one hand, it serves as *ortho*-directing group[29] allowing to regioselectively metalate the adjacent positions C4 and C6 with amide derived bases such as TMPMgCl·LiCl[44] and TMPLi.[40,146] On the other hand, it may easily be replaced by electrophiles such as iodine using a sulfoxide/magnesium exchange[33,34,38,40] and thus, gives access to further modifications of position 5. Hence, the previously obtained MOM-protected 7-azaindole **11** was selectively lithiated in position 2 using TMPLi in THF (-60 °C to -45 °C, 1 h), and chlorination with $PhSO_2Cl$[162] (**12d**) provided the dihalogenated 7-azaindole **19** in 82% yield, bearing a chloride substituent as C2-protecting group. Subsequent Br/Li exchange of **19** using *n*BuLi[108] (1.0 equiv, -78 °C, 5 min) and transmetalation with $MgCl_2$ (0.5 M in THF) furnished a *Grignard* reagent which reacted with 4-methoxy-3,5-dimethylbenzenesulfinyl chloride[40,172] (**20**) to give the desired azaindole derivative **21** in 90% yield. When this azaindole (**21**) was then subjected to magnesiation using TMPMgCl·LiCl (1.5 equiv, -30 °C, 10 min), a regioselective metalation occurred in position 4 and quenching with $(BrCl_2C)_2$ (**12e**)

[171] a) J. Chen, Q. Song, C. Wang, Z. Xi, *J. Am. Chem. Soc*. **2002**, *124*, 6238. b) K. Snegaroff, S. Komagawa, F. Chevallier, P. C. Gros, S. Golhen, T. Roisnel, M. Uchiyama, F. Mongin, *Chem. Eur. J.* **2010**, *16*, 8191. c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. d) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595. e) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, *72*, 6602.

[172] For the preparation of 4-methoxybenzenesulfinyl chloride, see: M. Peyronneau, N. Roques, S. Mazieres, C. Le Roux, *Synlett* **2003**, 631.

afforded the key azaindole **18**[173] in a quantitative yield of 97% (Scheme 69). Thus, the key precursor **18** was prepared in 48% yield over seven steps starting from commercially available pyridine **5**.

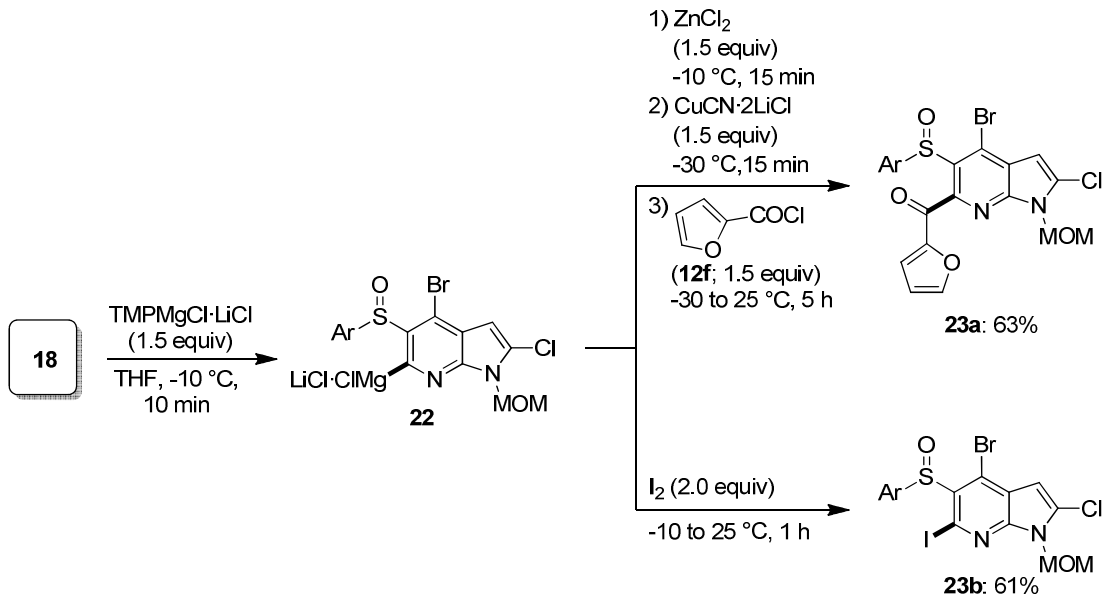


Scheme 69: Preparation of the polyfunctional key 7-azaindole precursor **18** *via* metalation and sulfinylation.

1.5 Regioselective Functionalization of Positions 6, 5 and 4 of the 7-Azaindole Scaffold

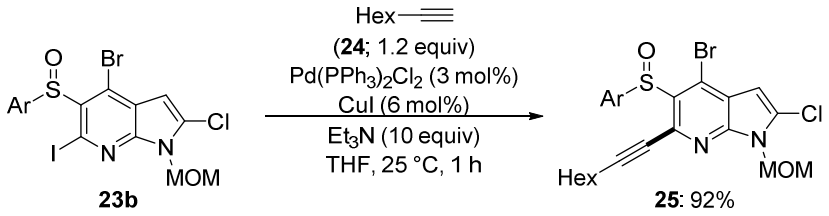
As mentioned before, the key azaindole precursor **18** bears hidden organometallic pathways which offer the selective and general functionalization of all five carbon positions of the 7-azaindole core. In this context, the sulfoxide group on C5 plays a major role, since it allows the directed *ortho*-metalation[29] of position 6. Thus, azaindole **18** was readily magnesiated on C6 using the chemoselective amide base TMPMgCl·LiCl[44] (1.5 equiv, -10 °C, 10 min) leading to the *Grignard* reagent **22**. This magnesium species was then transmetalated with $ZnCl_2$ (1 M in THF, 1.5 equiv) and subsequently reacted in a copper(I)-mediated acylation[160] (CuCN·2LiCl, 1 M in THF, 1.5 equiv) with furan-2-carbonyl chloride (**12f**) to furnish the heteroaroylated azaindole **23a**[173] in 63% yield (Scheme 55). Moreover, quenching of **22** with neat iodine provided the iodo-azaindole derivative **23b**[173] in 61% yield (Scheme 70).

[173] The regiochemistry of the products **18**, **23a**, **23b**, **27a**, **27b** and **37** was confirmed by X-ray crystallography, see: D. Appendix, Chapter 2.



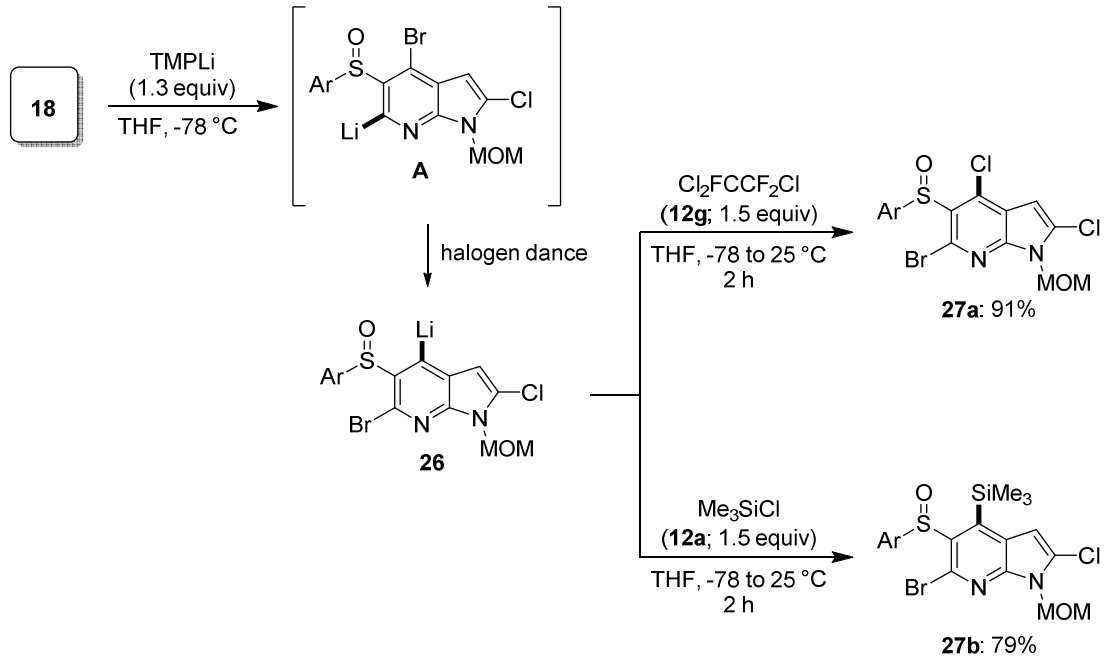
Scheme 70: Functionalization of position 6 *via* selective metalation using TMPMgCl·LiCl; Ar = 4-methoxy-3,5-dimethyl-phenyl.

Noteworthy, the iodide **23b** proved to be an excellent intermediate for further functionalization reactions. Thus, *Sonogashira* cross-coupling[96] of **23b** with 1-octyne (**24**) using $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%) and Et_3N (10 equiv) gave the desired alkyne **25** in 92% yield (Scheme 71).



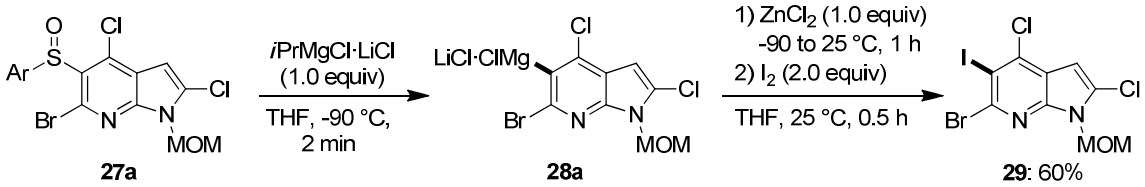
Scheme 71: *Sonogashira* cross-coupling of the iodide **23b** with 1-octyne (**24**); Ar = 4-methoxy-3,5-dimethyl-phenyl.

Interestingly, deprotonation of the azaindole derivative **18** with TMPLi (1.3 equiv, -78 °C) produced a transient lithium reagent (**A**) which underwent a halogen dance[166] leading to the 4-lithiated 7-azaindole **26** (Scheme 57). It was shown that the best yields for successive reactions were obtained when the lithium reagent was generated in the presence of the electrophile (*Barbier in situ*[164,165] conditions). Hence, performing the lithiation of **18** in the presence of 1,1,2-trichloro-1,2,2-trifluoroethane (Cl_2FCCF_2Cl ;**12g**, 1.5 equiv) gave the expected 4-chloro-7-azaindole **27a**[173] in 91% yield. Accordingly, in the presence of an excess of Me_3SiCl (**12a**) the silylated azaindole **27b**[173] was obtained in 79% yield (Scheme 72).



Scheme 72: Functionalization of position 4 *via* metalation using TMPLi under Barbier *in situ* conditions; Ar = 4-methoxy-3,5-dimethyl-phenyl.

The next functionalization was performed in position 5 *via* a sulfoxide/magnesium exchange.[33,34,38,40] Thus, treatment of **27a** with *i*PrMgCl·LiCl[32] (1.0 equiv) at -90 °C for 2 min[174] led to the magnesium species **28a** which was immediately subjected to transmetalation with $ZnCl_2$ followed by an iodolysis affording the iodide **29** in 60% yield (Scheme 73).

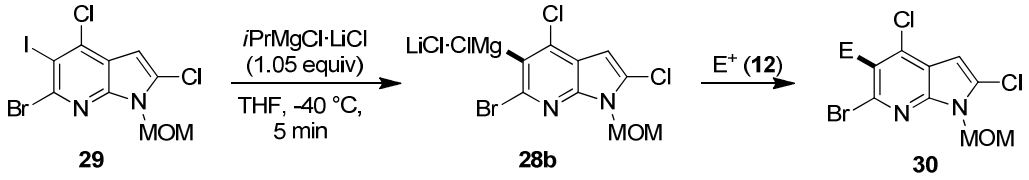


Scheme 73: Suloxide/magnesium exchange in position 5 using *i*PrMgCl·LiCl, and subsequent iodolysis; Ar = 4-methoxy-3,5-dimethyl-phenyl.

The iodide **29** was then conveniently converted to a magnesium reagent (**28b**) using *i*PrMgCl·LiCl (1.05 equiv, -40 °C, 5 min). This highly functionalized heterocyclic

[174] Noteworthy, this sulfoxide/magnesium exchange has to be performed at -90 °C within short time. At higher temperatures and longer reaction times, a competitive radical process with the solvent leads to extensive amounts of protonated species. This could as well not be overcome replacing THF by 2-methyl THF, since no reaction occurred between the sulfoxide moiety and *i*PrMgCl·LiCl. For more details on the competitive radical process, see: Ph.D. thesis Laurin Melzig, LMU Munich, **2011**, and Christian Bernhard Rauhut Ph.D. thesis, LMU Munich, **2008**.

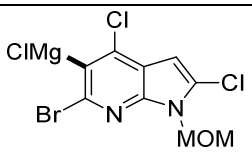
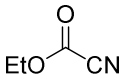
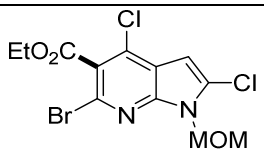
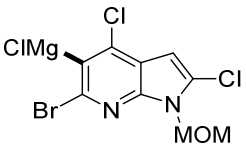
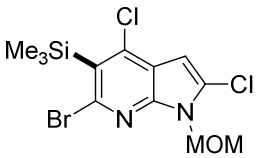
Grignard reagent **28b** readily undergoes various functionalization reactions furnishing the expected 5-subsituted 7-azaindoles of type **30** (Scheme 74 and Table 1).[175]



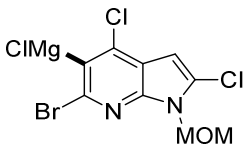
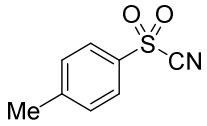
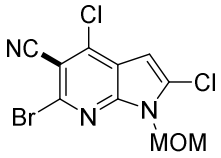
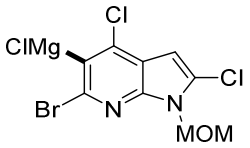
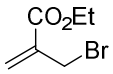
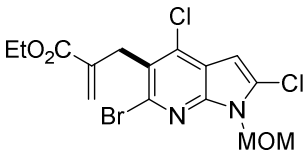
Scheme 74: Iodine/magnesium exchange in position 6 using *i*PrMgCl·LiCl, and subsequent functionalization.

Trapping the heterocyclic magnesium species **28b** with $NCCO_2Et$ (**12h**; 2.0 equiv) led to the desired ester **30a** in 95% yield (Table 1, entry 1). Similarly, reaction of **28b** with Me_3SiCl (**12a**; 10 equiv) furnishes the 5-silylated 7-azaindole **30b** in 97% yield (entry 2). Also, the *Grignard* reagent **28b** readily undergoes a trapping reaction using tosyl cyanide (TosCN; **12i**; 2.0 equiv) to afford the heterocyclic derivative **30c** in 68% yield (entries 3). A copper(I)-mediated allylation[160] in the presence of $CuCN \cdot 2LiCl$ using ethyl (2-bromomethyl)acrylate[159] (**12b**; 2.0 equiv) led to the expected 5-substituted azaindole **30d** in 78% yield (entry 4).

Table 1: Functionalization of position 5 of the 7-azaindole ring *via* the-magnesium reagent **28b**.

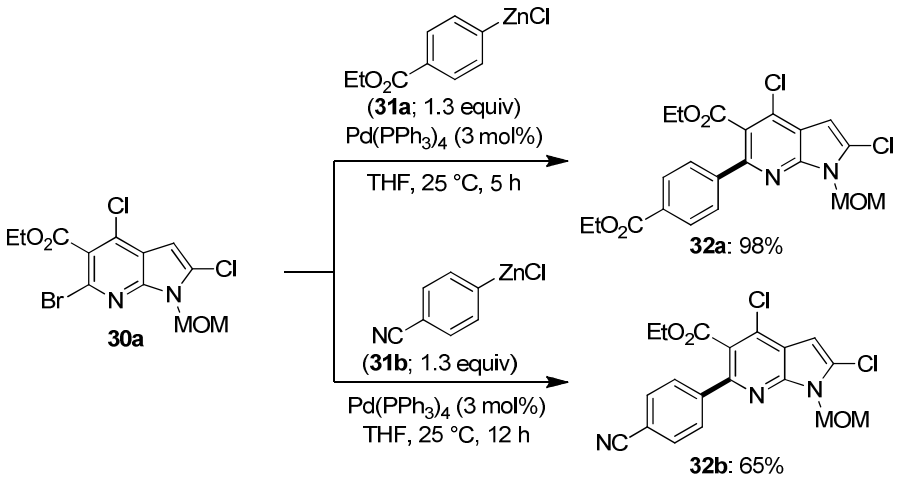
Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**28b**	**12h**	**30a**: 95%
		Me_3SiCl	
2	**28b**	**12a**	**30b**: 97%

[175] To avoid extensive protonations (see reference 174) the *Grignard* reagent **28a** obtained from compound **27a** had to be kept at low temperatures (-90 °C), which precludes effective quenching reactions with most electrophiles. Hence, the desired magnesium species (**28b**) was generated starting from the iodide **29**, since the exchange reaction could be performed at temperatures >-90 °C making subsequent functionalization reactions more convenient.

3	 **28b**	 **12i**	 **30c**: 68%
4	 **28b**	 **12b**	 **30d**: 78%[c]

[a] Obtained after I/Mg exchange reaction with *i*PrMgCl·LiCl (1.05 equiv) in THF at -40 °C in 5 min; additional complexed salts are omitted for sak of clarity. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after Cu-catalyzed allylation (CuCN·2LiCl (1.2 equiv) and ethyl(2-bromomethyl)acrylate (2.0 equiv)).

The 7-azaindole **30a** was then further functionalized in position 6 by performing *Negishi* cross-couplings[176] with *para*-substituted arylzinc reagents (1.30 equiv, **31a**: R = CO_2Et; **31b**: R = CN) in the presence of 3 mol% $Pd(PPh_3)_4$ (25 °C, 5-12 h) to furnish the 6-arylated azaindoles **32a-b** in 65-98% yield (Scheme 75).

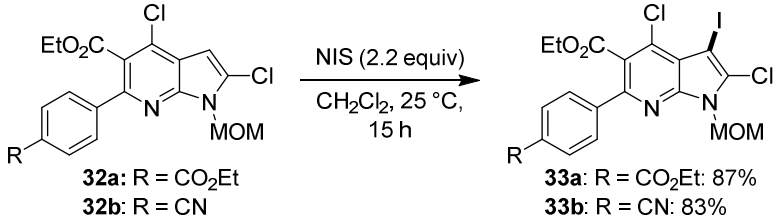


Scheme 75: Functionalization of position 6 *via Negishi* cross-coupling reactions with *para*-substituted arylzinc reagents; additional complexed salts are omitted for sake of clarity.

[176] a) A. King, N. Okukado, E.-i. Negishi, *J. Org. Chem.* **1977**, *42*, 1821. b) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. c) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. d) Ø. Rist, M. Begtrup, *J. Chem. Soc., Perkin Tran. 1* **2001**, 1566. e) X. Zeng, M. Quian, Q. Hu, E.-i. Negishi, *Angew. Chem. Int. Ed.* **2004**, *43*, 2259. f) E.-i. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang, in *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, 815. g) A. de Meijere, P. von Zezschwitz, S. Braese, *Acc. Chem. Res.* **2005**, *38*, 413. h) J.-X. Wang, J. McCubbin, M. Jin, R. Laufer, Y. Mao, A. Crew, M. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923. i) G. Manolikakes, M. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765. j) Z. Dong, G. Manolikakes, J. Li, P. Knochel, *Synthesis* **2009**, 681. k) G. Wang, N. Yin, E.-i. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118.

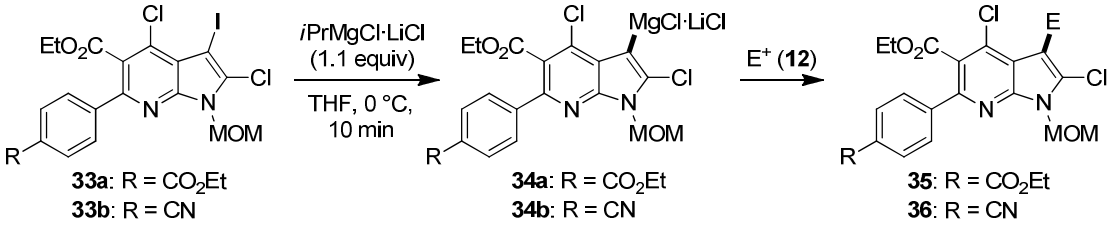
1.6 REGIOSELECTIVE FUNCTIONALIZATION OF POSITIONS 3 AND 2 OF THE 7-AZAINDOLE SCAFFOLD

After having performed various functionalization reactions for the modification of positions 6,5 and 4 of the 7-azaindole scaffold, the remaining unsubstituted position 3 of the heterocyclic derivatives **32a** and **32b** was regioselectively iodinatied using *N*-iodosuccinimide (NIS; 2.2 equiv) in CH_2Cl_2 at 25 °C within 15 h to afford the iodo-azaindoles **33a** and **33b** in 83-87% yield (Scheme 76).



Scheme 76: Iodination of position 3 using *N*-iodosuccinimide (NIS).

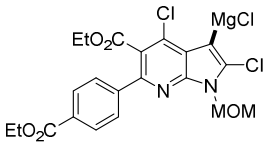
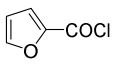
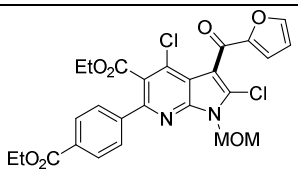
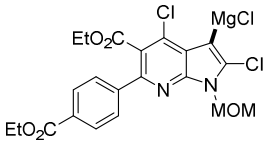
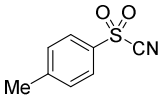
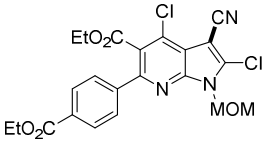
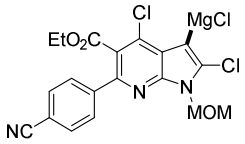
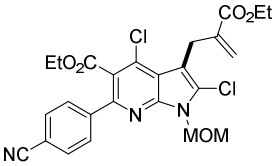
Subsequent I/Mg exchange using *i*PrMgCl·LiCl (1.1 equiv, -10 °C, 10 min) produced a magnesium species of type **34** which readily reacted with different electrophiles (Scheme 77 and Table 2).



Scheme 77: Iodine/magnesium exchange in position 3 using *i*PrMgCl·LiCl, and subsequent functionalization.

Thus, the *Grignard* reagent **34a** was subjected to a copper-mediated acylation[160] ($CuCN \cdot 2LiCl$, -30 to 25 °C, 16 h) with furan-2-carbonyl chloride (**12f**; 2.0 equiv) to furnish the desired aroylated azaindole **35a** in 68% yield (Table 2, entry 1). Similarly, after reaction of TosCN (**12i**; 1.5 equiv) the nitrile **35b** was obtained in 84% yield (entry 2). Also, after transmetalation with $ZnCl_2$, the magnesium species **34b** smoothly underwent a copper-mediated allylation[160] with ethyl(2-bromomethyl)acrylate[159] (**12b**; 1.2 equiv) to produce the expected heterocycle **36** in 69% yield (entry 3).

Table 2: Functionalization of position 3 of the 7-azaindole ring *via* the magnesium reagents **34a-b**.

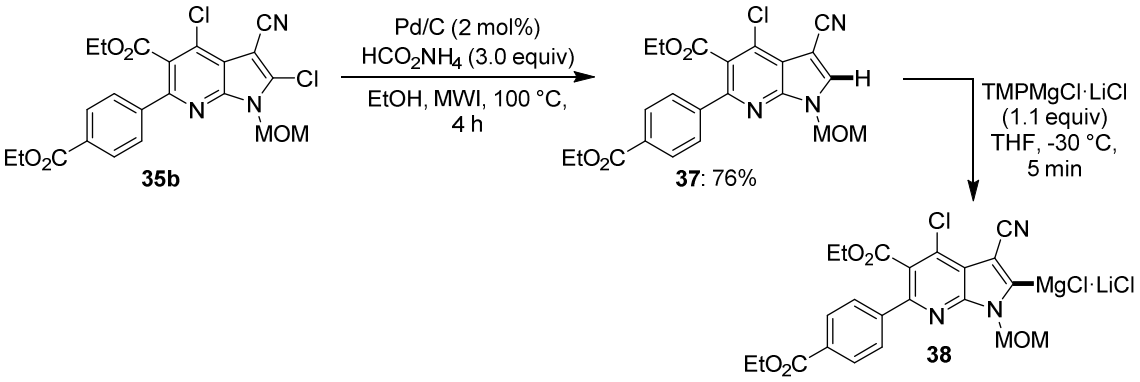
Entry	Mg-Reagent[a]	Electrophile	Product, Yield[b]
			
1	**34a**	**12f**	**35a**: 68%[c]
			
2	**34a**	**12i**	**35b**: 84%
			
3	**34b**	**12b**	**36**: 69%[d]

[a] Obtained after I/Mg exchange reaction with *i*PrMgCl·LiCl (1.1 equiv) in THF at 0 °C in 10 min; additional complexed salts are omitted for sake of clarity. [b] Yield of analytically pure isolated product as determined by ^{1}H NMR analysis. [c] Obtained after Cu-mediated acylation (CuCN·2LiCl (1.2 equiv) and furan-2-carbonyl chloride (1.5 equiv)). [d] Obtained after Cu-mediated allylation (CuCN·2LiCl (1.2 equiv) and ethyl(2-bromomethyl)acrylate (1.2 equiv)).

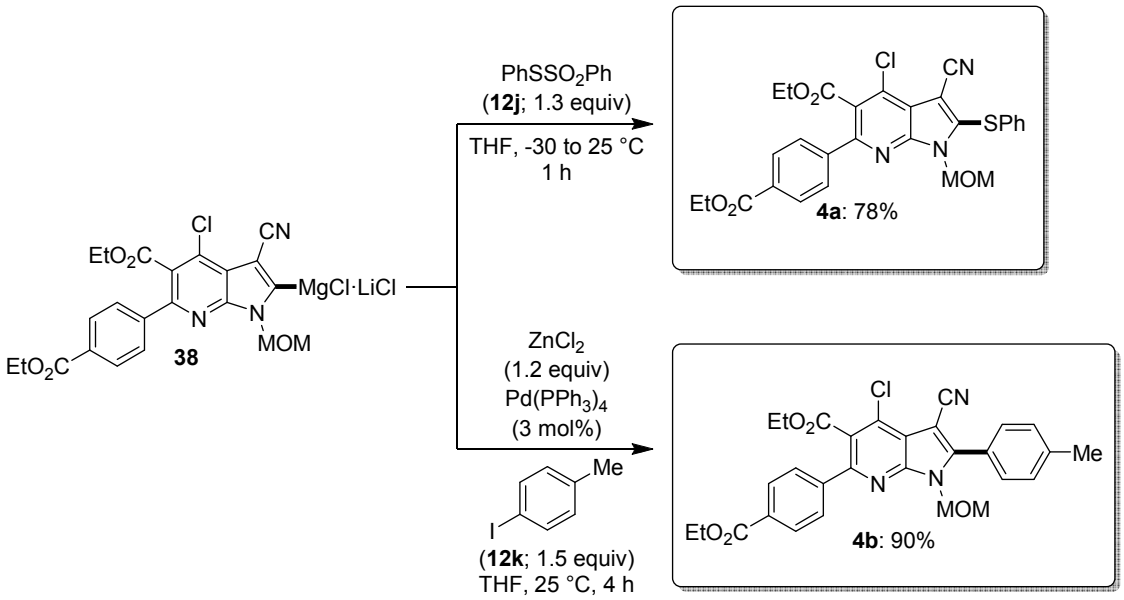
To be able to functionalize position 2 of the 7-azaindole scaffold, the chloride substituent, which served as protecting group, had to be removed. To this end, we performed a dechlorination of **35b**[177] according to the *Schlosser* method[178] using 3.0 equiv of HCO_2NH_4 in the presence of 2 mol% Pd/C under microwave irradiation (MWI, 100 °C, 4 h) providing the monochlorinated azaindole **37**[173] in 76% yield (Scheme 78).

The so-obtained heterocycle **37** was then subjected to a metalation with TMPMgCl·LiCl (1.1 equiv, -30 °C, 5 min) affording the *Grignard* reagent **38** (Scheme 78). This magnesium reagent readily reacted with $PhSSO_2Ph$ (**12j**; 1.3 equiv) to give the fully dressed thioether **4a** in 78% yield. Similarly, transmetalation of **38** with $ZnCl_2$ (1.2 equiv) and subsequent *Negishi* cross-coupling[176] using 4-iodotoluene (**12k**; 1.5 equiv) in the presence of 3 mol% $Pd(PPh_3)_4$ furnished the full-functionalized azaindole **4b** in 90% yield (Scheme 79).

[177] A direct zinc insertion into the Cl-C-bond of **35b** did not lead to a 2-zincated azaindole derivative.
[178] a) C. Bobbio, T. Rausis, M. Schlosser, *Chem. Eur. J.* **2005**, *11*, 1903. b) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009.



Scheme 78: Dechlorination in position 2 using the *Schlosser* method and subsequent magnesiation using TMPMgCl·LiCl.

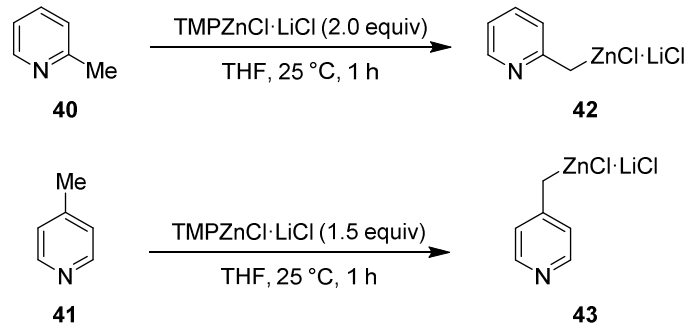


Scheme 79: Functionalization of the *Grignard* reagent **38** in position 2.

2. PREPARATION AND REACTIONS OF HETEROARYLMETHYLZINC REAGENTS

2.1 INTRODUCTION

Organozinc derivatives are of key importance in organic synthesis and have found numerous applications.[9,179,180] Owing to the rather covalent character of the carbon-zinc bond, these organometallic reagents show a high functional group tolerance and thus, allow the preparation of polyfunctionalized organozinc compounds. In this context, a broad range of (hetero)aryl-,[15,64,65] alkyl-,[58b] alkenyl-[181] and allylzinc[182] reagents has been successfully prepared and reacted with various electrophiles. Recently, *Metzger* and *Knochel* established a method for the direct zinc insertion of metallic zinc dust into benzylic chlorides mediated by LiCl.[56b] With heterocycles displaying a major part of building blocks in pharmaceuticals and materials, we envisioned the development of a protocol for the convenient and general preparation of heteroarylmethylzinc reagents. Generally, there are two strategies which could be applied for the synthesis of heteroarylmethylzinc reagents. The first strategy involves the metalation of methylated heterocycles such as 2- and 4-picolines with different bases.[183] In this context, *Duez* and *Knochel* have recently shown that treatment of 2-picoline (**40**) and 4-picoline (**41**) with TMPZnCl·LiCl readily furnishes the zincated picolines **42** and **43** (Scheme 80).[183c]

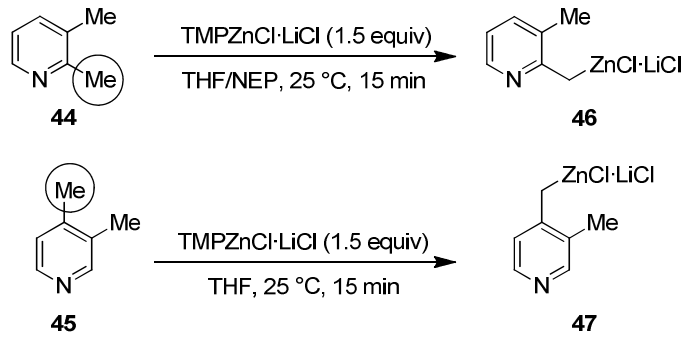


Scheme 80: Zincation of 2-picoline (**40**) and 4-picoline (**41**) using TMPZnCl·LiCl.

However, if this metalation strategy is applied to 3-picolines, several difficulties occur. On the one hand, the resulting cross-conjugated anion is rather unstabilized and thus, highly reactive. In contrary to zincated 2- and 4-picolines, the negative charge is not delocalized over the pyridyl nitrogen atom. On the other hand, mostly lithium amide

[179] a) H. Duan, L. Meng, D. Bao, H. Zhang, Y. Li, A. Lei, *Angew. Chem. Int. Ed*. **2010**, *49*, 6387. b) S. Bernhardt, S. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205. c) L. E. Zimmer, A. Charette, *J. Am. Chem. Soc*. **2009**, *131*, 15633.
[180] a) E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738. b) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[181] C. Sämann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.
[182] C. Sämann, P. Knochel, *Synthesis* **2013**, *45*, 1870.
[183] a) T. Kamienski, P. Gros, Y. Fort, *Eur. J. Org. Chem.* **2003**, 3855. b) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161. c) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686.

derived bases such as LDA[105] are necessary to successfully metalate 3-picolines, precluding the presence of a wide range of functional groups.[184] Metalation of the methyl moiety in 3-picoline using TMPZnCl·LiCl does not lead to satisfactory results. In fact, when 2,3-lutidine (**44**) and 3,4-lutidine (**45**) are treated with the zinc base, zincation occurs in 2- and 4-position, respectively, leading to zinc derivatives **46** and **47**, while the 3-position stays untouched (Scheme 81).[183c]

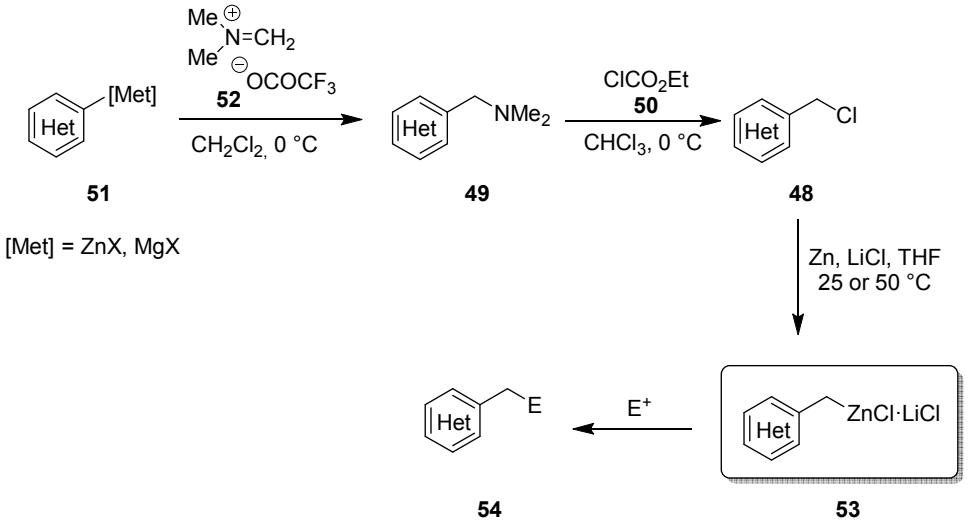


Scheme 81: Zincation of 2,3-lutidine (**44**) and 3,4-lutidine (**45**) using TMPZnCl·LiCl; NEP = *N*-ethylpyrrolidone.

Thus, a different method for the general preparation of heteroarylmethylzinc reagents had to be chosen. To this end, influenced by *Metzger*'s strategy of the LiCl-promoted direct zinc insertion into benzylic chlorides,[56b] we decided to use chloromethyl heteroarenes as precursors for the synthesis of such organozinc reagents which should as well be obtained by oxidative zinc insertion. Yet, common strategies for the synthesis of chloromethyl (hetero)arenes include the chlorination of benzylic alcohols using reagents such as phosphorus pentachloride, phosphoryl chloride and thionyl chloride. It is known that during these chlorination reactions mentionable amounts of HCl are formed.[185] In case of nitrogen-containing heterocycles such as pyridines, pyrimidines or quinolines, this acidic environment might cause protonation of the heterocycles or lead to decomposition and unwanted side reactions, which makes those protocols inefficient when it comes to the preparation of chloromethyl heteroarenes. We therefore envisioned preparing these heteroarylmethyl chlorides (**48**) from the appropriate "heterobenzylic" dimethylamines (**49**) by a literature-known procedure which describes the conversion of dimethylamines to the corresponding chlorides using ethyl chloroformate (**50**).[186] In this context, the analogous "heterobenzylic" dimethylamines should be synthesized by a homologation reaction of heteroarylmagnesium and -zinc reagents of type **51** with the

[184] M. Albrecht, C. Riether, *Synlett* **1995**, 309.
[185] a) M. Yoshihara, T. Eda, K. Sakaki, T. Maeshima, *Synthesis* **1980**, *9*, 746. b) R. M. Carman, I. M. Shaw, *Aust. J. Chem.* **1976**, *29*, 133. c) F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry, D. Tschaen, *J. Org. Chem.* **2008**, *73*, 312.
[186] D. S. Kashdan, J. A. Schwartz, H. Rapoport, *J. Org. Chem.* **1982**, *47*, 2638 and references cited therein.

Mannich's ion[187] methylene(dimethyl)iminium trifluoroacetate **52**[188] generated by reaction of *N*,*N*,*N*',*N*'-tetramethylmethanediamine with trifluoroacetic anhydride. Having prepared the appropriate chloromethyl heteroaryl precursors **48**, we then envisioned to perform a direct LiCl-mediated zinc insertion into these heteroarylmethyl chlorides (**48**) to obtain zinc reagents of type **53**, which should be employed in subsequent reactions with electrophiles to furnish heterocyclic products of type **54** (Scheme 82).



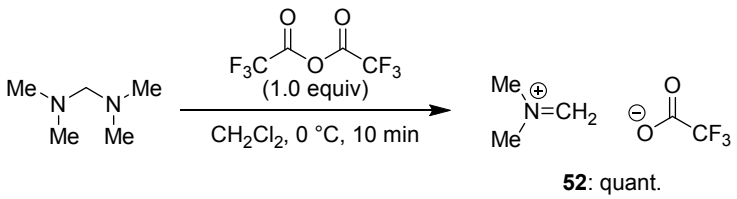
Scheme 82: Preparation of chloromethyl heterocycles of type **48**, their conversion to zinc reagents of type **53**, and subsequent functionalizations leading to products of type **54**; X = Cl·LiCl, Br·LiCl.

2.2 PREPARATION OF (DIMETHYLAMINO)METHYL HETEROARENES

For a general preparation of heteroarylmethylzinc reagents, the first step consisted in the synthesis of (dimethylamino)methyl heteroarenes (**49**) by reaction of heterocyclic organometallics (**51**) with the *Mannich*'s ion **52**. Thereby, **52** is prepared by reaction of *N*,*N*,*N*',*N*'-tetramethylmethanediamine with trifluoroacetic anhydride in anhydrous CH_2Cl_2 at 0 °C (Scheme 83).

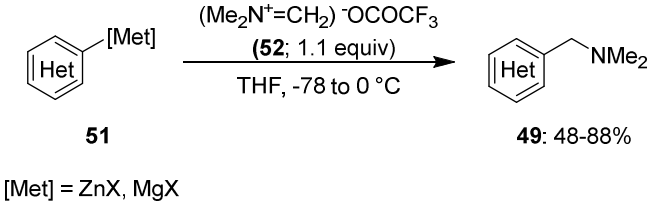
[187] For a recent review on the *Mannich* reaction, see: J. L. Li, *Name Reactions for Homologations*, **2009**, *2*, 653.

[188] a) N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941. b) N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, 2143 and references cited therein. For the synthesis of *Mannich*'s ions in anhydrous media with different counter ions, see: c) A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, P. Potier, *J. Am. Chem. Soc.* **1968**, *90*, 5622. d) G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239. e) D. Grierson, *Org. React.* **1990**, *39*. f) M. Gaudry, Y. Jasor, T. B. Khac, *Org. Synth.* **1988**, *6*, 474.



Scheme 83: Anhydrous preparation of the *Mannich*'s ion **52**.

Various heteroarylmagnesium and -zinc reagents of type **51** reacted with the *Mannich*'s ion **52** at low temperatures to furnish the corresponding dimethylamines **49** in good yields (Scheme 84 and Table 3).

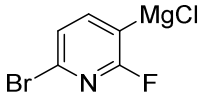
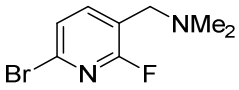
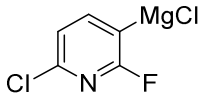
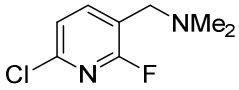
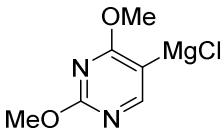
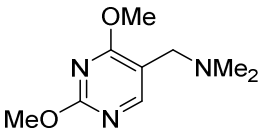
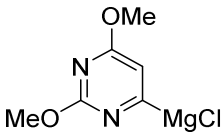
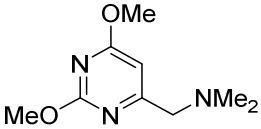
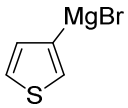
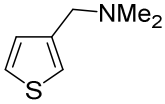
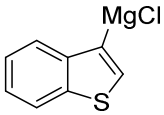
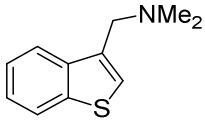
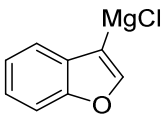
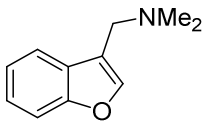
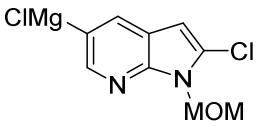
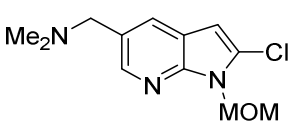


Scheme 84: Preparation of (dimethylamino)methyl heteroarenes of type **49** by reaction of **52** with organometallic compounds of type **51**.

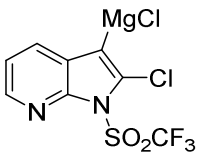
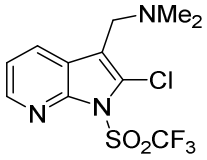
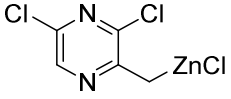
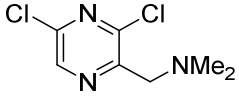
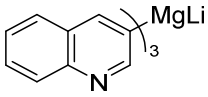
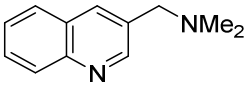
Thus, the pyridyl magnesium reagents **51a** and **51b** readily reacted with methylene(dimethyl)iminium trifluoroacetate **52** to afford the dimethylamines **49a** and **49b**[189] in 79-86% yield (Table 3, entries 1 and 2). Similarly, the regioisomeric dimethoxy-pyrimidines **51c** and **51d** were smoothly converted to the corresponding (dimethylamino)methyl heteroarenes **49c** and **49d** in 83% and 79% yield, respectively (entries 3 and 4). Also, the *Grignard* reagents **51e-g** were efficiently treated with the *Mannich*'s ion **52** to furnish the amines **49e-g** in 60-78% yield (entries 5-7).[190] The 7-azaindolyl magnesium species **51h** and **51i** successfully reacted with **52** to give the corresponding 5- and 3-(dimethylamino)methyl azaindoles **49h** and **49i** in 48-88% yield (entries 8 and 9). In the same manner, the pyrazine derivative **49j** and the quinolyl amine **49k** were readily obtained in 51-70% yield (entries 10 and 11).

[189] These experiments were conducted by G. A. Monzón Díaz and are given here for sake of completeness. For further experimental details, see: Ph.D. thesis Gabriel Andrés Monzón Díaz, LMU Munich, **2012**.
[190] These experiments were conducted by A. J. Wagner and are given here for sake of completeness. For further experimental details, see: Ph.D. thesis Andreas Johannes Wagner, LMU Munich, **2011**.

Table 3: Preparation of (dimethylamino)methyl heteroarenes of type **49** by reaction of **52** with organometallic compounds of type **51**.

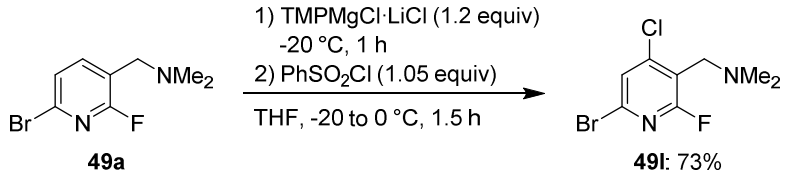
Entry	Heteroaryl Organometallic[a],[191]	Product, Yield[b]
		
1	**51a**	**49a**: 86%
		
2	**51b**	**49b**: 79%[189]
		
3	**51c**	**49c**: 83%
		
4	**51d**	**49d**: 79%
		
5	**51e**	**49e**: 60%[190]
		
6	**51f**	**49f**: 78%[190]
		
7	**51g**	**49g**: 70%[190]
		
8	**51h**	**49h**: 48%

[191] For experimental details on the preparation of the corresponding heterocyclic organometallics, please refer to: C. Experimental Section.

9	 **51i**	 **49i**: 88%
10	 **51j**	 **49j**: 51%
11	 **51k**	 **49k**: 70%

[a] Additional complexed salts are omitted for sake of clarity. [b] Yield of isolated, analytically pure product.

Since the (dimethylamino)methyl moiety is known to serve as directing group,[29,167-169] the amino derivative **49a** could smoothly be metalated using TMPMgCl·LiCl[44] (1.2 equiv, -20 °C, 1 h). Subsequent chlorination with $PhSO_2Cl$[162] (1.05 equiv) afforded the polyfunctional pyridine **49l** in 73% yield (Scheme 85).[192]

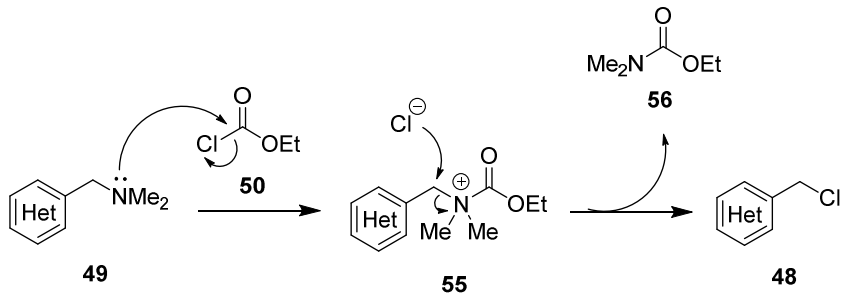


Scheme 85: *Ortho*-magnesiation of pyridyl amine **49a** using TMPMgCl·LiCl.

2.3 PREPARATION OF CHLOROMETHYL HETEROARENES

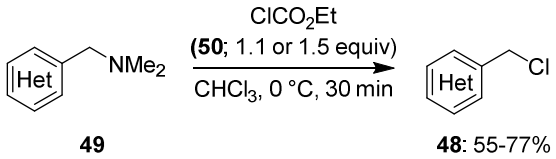
The thus prepared (dimethylamino)methyl heteroarenes of type **49** were then subjected to chlorination using ethyl chloroformate (**50**) to give the corresponding chloromethyl heterocycles of type **48**.[186] The mechanism of this chlorination reaction is outlined in Scheme 86. Under liberation of a chloride anion, the heterocyclic amine **49** attacks the electrophilic center of ethyl chloroformate (**50**) to form the acylammonium ion **55**. The latter is then attacked by the chloride anion to form the "heterobenzylic" chloride **48**, while expelling ethyl *N*,*N*-dimethylcarbamate **56** being the driving force of this reaction.

[192] For more examples on the *ortho*-metalation of (dimethylamino)methyl heteroarenes, see: Ph.D. thesis Andreas Johannes Wagner, LMU Munich, **2011**, and Ph.D. thesis Gabriel Andrés Monzón Díaz, LMU Munich, **2012**.



Scheme 86: Mechanism of the conversion of (dimethylamino)methyl heteroarenes of type **49** to the corresponding chloromethyl heterocycles **48** using ethyl chloroformate (**50**).

Thus, at 0 °C the (dimethylamino)methyl heteroarenes of type **49** are treated with ethyl chloroformate (**50**; 1.1 or 1.5 equiv) in chloroform to furnish the corresponding chloromethyl derivatives of type **48** in 55-77% yield after 30 min reaction time (Scheme 87 and Table 4).

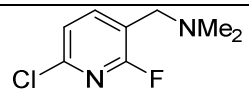
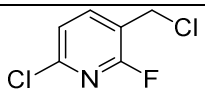
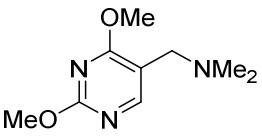
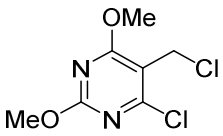
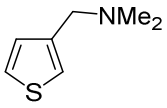
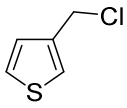
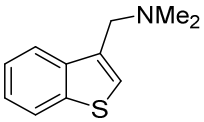
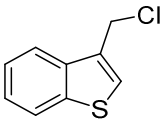
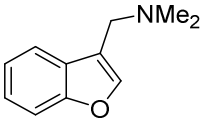
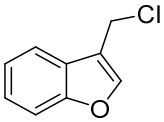


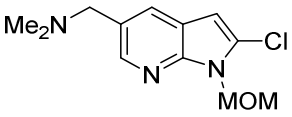
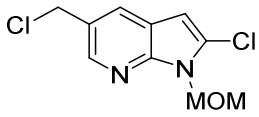
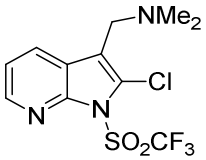
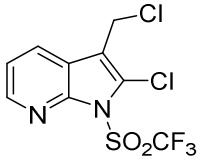
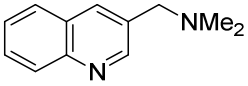
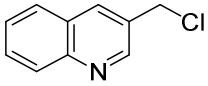
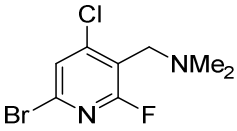
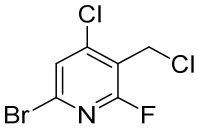
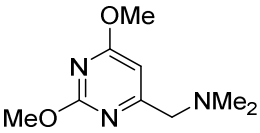
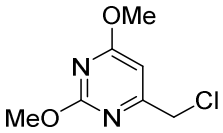
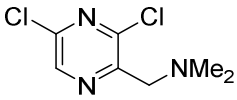
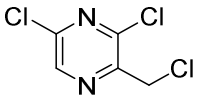
Scheme 87: Preparation of chloromethyl heterocycles of type **48** by reaction of (dimethylamino)methyl heteroarenes **49** with ethyl chloroformate (**50**).

In that manner, the dimethylamine **49b** was treated with **50** (1.1 equiv, 0 °C, 0.5 h) in chloroform to afford the corresponding chloride **48a** in 60% yield (Table 4, entry 1).[189] Noteworthy, the pyrimidine derivative **49c** could be further *ortho*-metalated with TMPMgCl·LiCl (1.1 equiv, 25 °C, 45 min), subsequently trapped with 1,1,2-trichlorotrifluoroethane (1.1 equiv, 50 °C, 4 h) and then subjected to chlorination using ethyl chloroformate (**50**; 1.1 equiv, 0 °C, 0.5 h) to furnish the full functionalized heterocycle **48b** in 55% overall yield (entry 2).[189] Also, the (dimethylamino)methyl heteroarenes **49e-g** were successfully converted to the "heterobenzylic" chlorides **48c-e** in 71-77% yield using 1.1 equiv of **50** at 0 °C for 30 min (entries 3-5).[190] The 7-azaindole derivatives **49h** and **49i** reacted with ethyl chloroformate (**50**, 1.5 equiv, 0 °C, 0.5 h) to give the expected chlorides **48f** and **48g** in 59% and 73% yield, respectively (entries 6 and 7). Similarly, the quinolyl derivative **48h** could be obtained in 60% yield from the corresponding amine **49k** (entry 8). Noteworthy, for an efficient transformation of dimethylamine **49l** to the heteroarylmethyl chloride **48i**, the reaction had to be heated to 70 °C for 2 h. After 0.5 h at 0 °C, a sluggish reaction mixture was obtained indicating the formation of a salt, probably an acylammonium ion of type **55**, which did not react any further. Thus, no formation of the corresponding product could be detected *via* GC/MS.

Luckily, upon heating, the reaction could be driven to completion, furnishing the expected chloromethyl heterocycle **48i** in 67% yield (entry 9). Also, when the pyrimidyl amine **49c** was treated with $ClCO_2Et$ (**50**; 1.5 equiv, 0 °C, 0,5 h), a sluggish reaction mixture was obtained containing mainly the corresponding acylammonium ion. However, heating the reaction did not lead to any improvement and only traces of the desired chloride **48j** could be detected on GC/MS. Any attempts in breaking this ionic structure by addition of excess of **50** or a naked chloride ions such as *tert*-butylammonium chloride, by refluxing the reaction mixture or by changing the solvent to *N*,*N*'-dimethylpropyleneurea (DMPU) did not result in an efficient formation of the corresponding chloromethyl derivative **48j** (entry 10). In the same way, the pyrazyl chloride **48k** could not be obtained applying our strategy (entry 11). Here, the major problem was also the formation of a rather stable ammonium ion of type **55**, which did not react further to the corresponding chloride under any attempts.

Table 4: Preparation of chloromethyl heteroarenes of type **48** by reaction of **50** with (dimethylamino)methyl heterocycles of type **49**.

Entry	Heterocyclic Amine	Product, Yield[a]
		
1	**49b**	**48a**: 60%[189]
		
2	**49c**	**48b**: 55%[189]
		
3	**49e**	**48c**: 71%[190]
		
4	**49f**	**48d**: 72%[190]
		
5	**49g**	**48e**: 77%[190]

6		**49h**		**48f**: 59%
7		**49i**		**48g**: 88%
8		**49k**		**48h**: 60%
9		**49l**		**48i**: 67%[b]
10		**49c**		**48j**: decomp.
11		**49j**		**48k**: decomp.

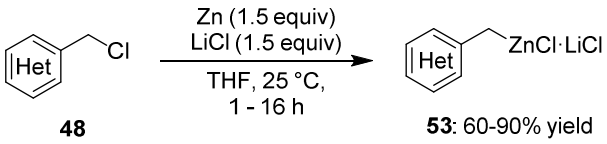
[a] Yield of isolated, analytically pure product. [b] Reaction was performed at 70 °C for 2 h.

2.4 PREPARATION AND REACTIONS OF HETEROARYLMETHYLZINC REAGENTS

2.4.1 LICL-PROMOTED ZINC INSERTION INTO CHLOROMETHYL HETEROARENES

Applying the method recently reported by *Metzger* and *Knochel*,[56b] we envisioned to prepare various heteroarylmethylzinc reagents of type **53** by a LiCl-mediated zinc insertion into the corresponding chloromethyl heteroarenes of type **48**. To this end, commercially available zinc dust was treated with 1,2-dibromoethane and chlorotrimethylsilane prior to insertion into the "heterobenzylic" chlorides **48**. In this manner, a broad range of chloromethyl heteroarenes (**48**) was successfully converted to the zinc compounds **53** within 1-16 h at 25 °C determining the appropriate yields of active species by iodometric titration[193] (Scheme 88 and Table 5).

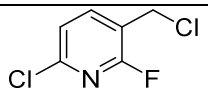
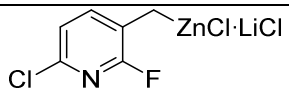
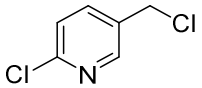
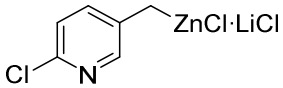
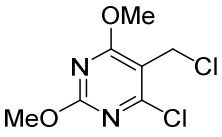
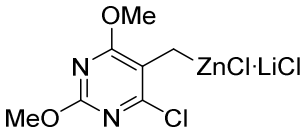
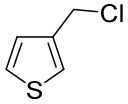
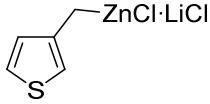
[193] A. Krasovskiy, P. Knochel *Synthesis* **2006**, 890.



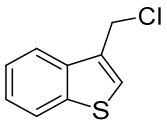
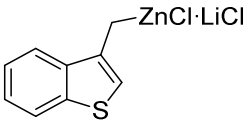
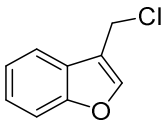
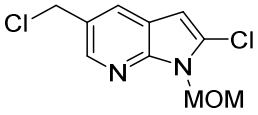
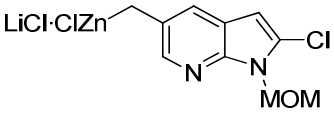
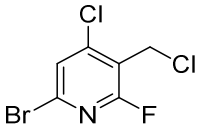
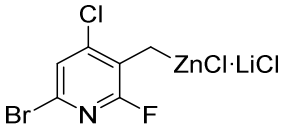
Scheme 88: Preparation of heteroarylmethylzinc reagents of type **53** *via* direct LiCl-promoted oxidative insertion using zinc dust.

Hence, the previously prepared pyridyl derivative **48a** was readily converted to the corresponding zinc reagent **53a** in 85% yield after 1 h at 25 °C (Table 5, entry 1).[189] Similarly, the pyridylzinc reagent **53b** could be obtained from commercially available 2-chloro-5-(chloromethyl)pyridine (**48l**) in 80% yield (entry 2).[190,194] The pyrimidyl chloride **48b** was smoothly subjected to zinc insertion affording **53c**[189] in 71% yield (entry 3). Also, the *S*- and *O*-heterocycles **48c-e** furnished the corresponding zinc organyls **53d-f** in 77-81% yield after 12-16 h at 25 °C (entries 4-6).[190] In that fashion, the 7-azaindolylzinc compound **53g** and the polyfunctional pyridyl derivative **53h** were obtained in 60-90% yield (entries 7 and 8).

Table 5: Preparation of heteroarylmethylzinc reagents of type **53** by direct LiCl-promoted zinc insertion into chloromethyl heteroarenes of type **48**.

Entry	Heterocyclic Chloride	Product (t, Yield[a])
		
1	**48a**	**53a** (1 h, 85%)[189]
		
2	**48l**	**53b** (2.5 h, 80%)[190]
		
3	**48b**	**53c** (1 h, 71%)[189]
		
4	**48c**	**53d** (12 h, 78%)[190]

[194] In this context, the introduction of a chlorine substituent in position 6 of the pyridine core seems to be crucial for a successful transformation to the corresponding zinc organyl, since unsubstituted 3-(chloromethyl)pyridine rapidly polymerizes when subjected to zinc insertion. For more details, see: Ph.D. thesis Andreas Johannes Wagner, LMU Munich, **2011**. For the use of **53b** in Pd-catalyzed acylations, see: K.-H. Cho, S.-H. Kim, *Bull. Korean Chem. Soc.* **2013**, *34*, 983.

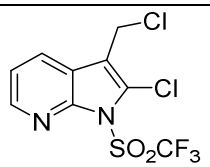
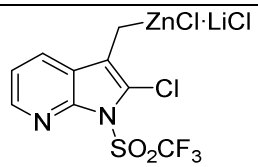
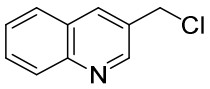
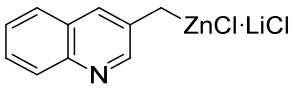
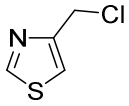
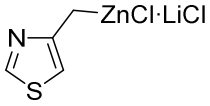
5		**48d**		**53e** (16 h, 77%)[190]
6		**48e**		**53f** (16 h, 81%)[190]
7		**48f**		**53g** (2.5 h, 60%)[b]
8		**48i**		**53h** (1 h, 90%)

[a] Active yield determined by iodometric titration. [b] Reaction was performed at 50 °C.

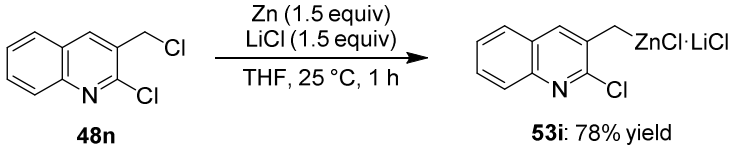
However, all attempts converting the azaindole derivative **48g** to an active organometallic species led to unsatisfactory results. No reaction could be detected *via* GC/MS or thin layer chromatography when **48g** was treated with activated zinc and LiCl in THF at 50 °C for 3 d (Table 6, entry 1). Changing the solvent for the zinc insertion to the higher boiling DMPU and heating the reaction mixture to 90 °C for 3 d only led to unreacted starting material. When azaindole **48g** was subjected to the more powerful LiCl-promoted magnesium insertion in the presence or absence of $ZnCl_2$,[23,58] besides unreacted substrate, partial reduction and loss of the N1-protecting group were the results. For quinoline derivative **48h** (entry 2) and the 4-(chloromethyl)thiazole **48m**[195] (entry 3), oxidative zinc insertion at 25 °C led to decomposition due to partial polymerization.

[195] Obtained by washing commercially available 4-(chloromethyl)thiazole hydrochloride with potassium hydroxide and extracting the aqueous phase with diethyl ether.

Table 6: Decomposition or reduction reactions upon zinc insertion.

Entry	Heterocyclic Chloride	Product
		
1	**48g**	no reaction
		
2	**48h**	decomp.
		
3	**48m**	decomp.

In case of the heteroarene **48h**, this problem could be overcome by introducing a chlorine substituent in position 2. Thus, 2-chloro-3-(chloromethyl)quinoline **48n**[196] was successfully converted to the corresponding zinc reagent **53i** in 78% yield after 1 h at 25 °C (Scheme 89).

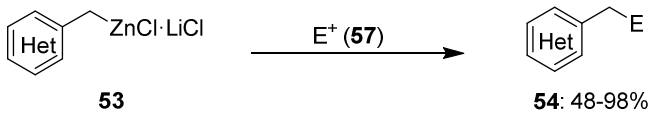


Scheme 89: Preparation of quinolylzinc reagent **53i** *via* LiCl-promoted oxidative zinc insertion into chloromethyl quinoline **48n**.

2.4.2 REACTION OF HETEROARYLMETHYLZINC REAGENTS WITH ELECTROPHILES

With a broad range of zinc reagents of type **53** in hand, various reactions were performed including Pd-catalyzed *Negishi* cross-couplings,[176] Cu-mediated acylations,[160] Cu-catalyzed allylations,[160] and addition reactions to *S*-benzenesulfonothioates[197] and aldehydes, affording the corresponding heterocyclic products of type **54** (Scheme 90 and Table 7).

[196] Prepared in two steps from commercially available 2-chloro-3-formylquinoline in an overall yield of 72% according to: S. Kumar, D. Kaushik, S. Bawa, S. A. Khan, *Chem. Biol. Drug Des.* **2012**, *79*, 104.
[197] For the general preparation of *S*-benzenesulfonothioates, see: K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, *3*, 343.

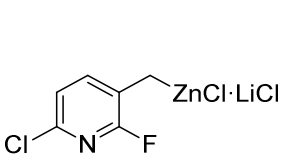
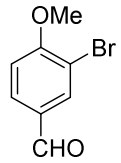
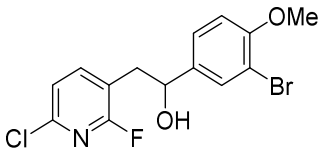
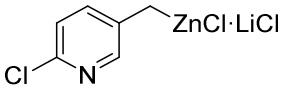
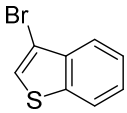
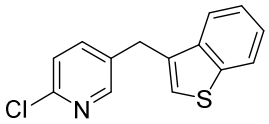
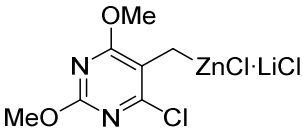
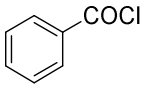
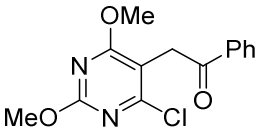
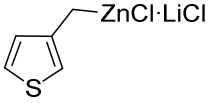
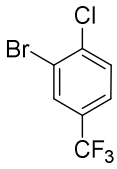
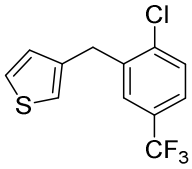
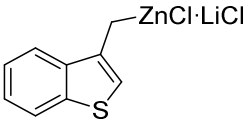
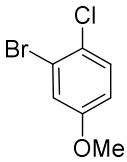
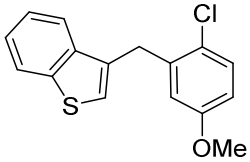
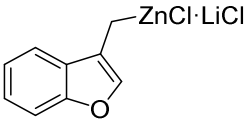
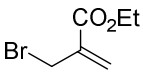
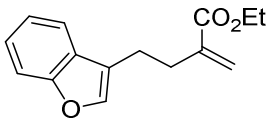
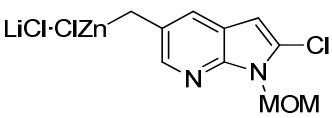
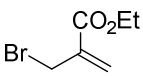
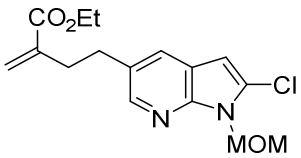
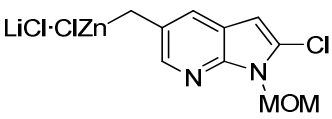
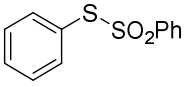
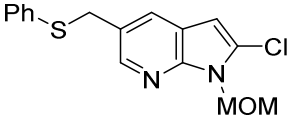


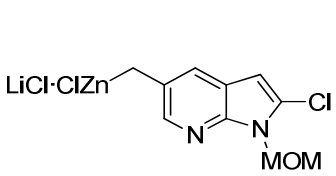
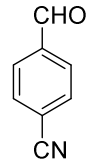
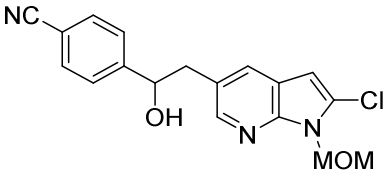
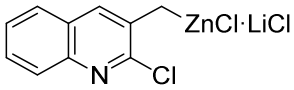
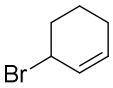
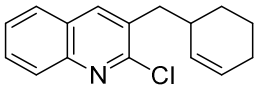
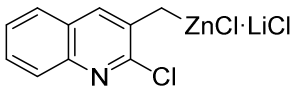
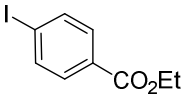
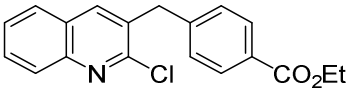
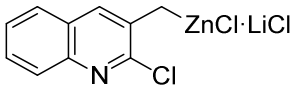
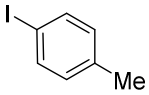
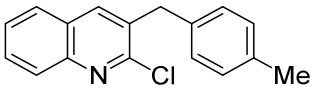
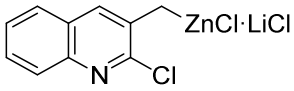
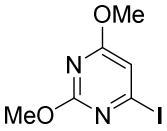
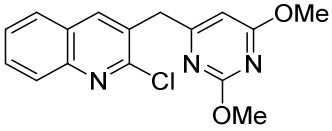
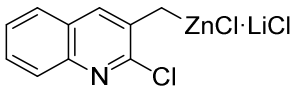
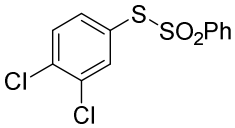
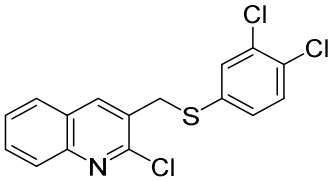
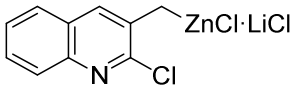
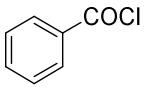
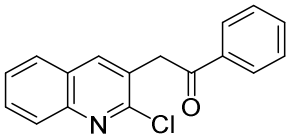
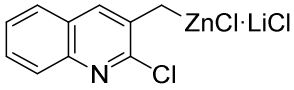
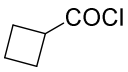
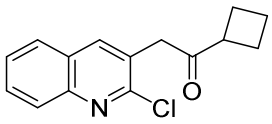
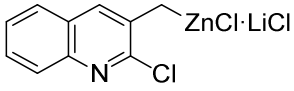
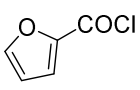
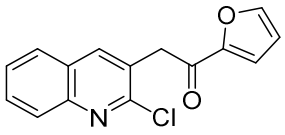
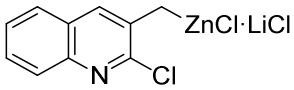
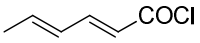
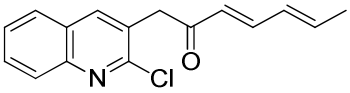
Scheme 90: Reaction of heteroarylmethylzinc reagents of type **53** with electrophiles (**57**) to afford products of type **54**.

In that manner, a summary of the thus obtained functionalized heterocycles **54** is shown in Table 7. Hence, the polyfunctional pyridyl reagent **53a** readily reacted with the aldehyde **57a** (0.85 equiv) to give the alcohol **54a** in 80% yield (Table 7, entry 1).[189] Similarly, in the presence of 1 mol% PEPPSI-IPr[198] the zinc reagent **53a** was successfully subjected to a *Negishi* cross-coupling[176] with the aryl bromide **57b** (0.9 equiv) to furnish the substituted pyridine **54b** in 93% yield (entry 2).[190] The pyrimidine derivative **53c** was smoothly converted to the corresponding functionalized heterocycle **54c** in 88% yield performing a copper-mediated acylation[160] (1.2 equiv CuCN·2LiCl) using benzoyl chloride (**57c**; 0.9 equiv; entry 3). [189] The *S*-heterocyclic zinc reagents **53d** and **53e** smoothly reacted with aryl bromides **57d** and **57e** (0.9 equiv) using 1 mol% PEPPSI-IPr to give **54d** and **54e** in 72-85% yield (entries 4 and 5).[190] After a copper-mediated allylation (5 mol% CuCN·2LiCl) with ethyl(2-bromomethyl)acrylate[159] (**57f**; 0.9 equiv), the benzofuryl derivative **54f**[190] and the azaindole **54g** were obtained in 80 and 98% yield, respectively (entries 6 and 7). Also, the 7-azaindolylzinc reagent **53g** readily added to *S*-benzenesulfonothioate (**57g**; 0.9 equiv) and 4-cyanobenzaldehyde (**57h**; 0.9 equiv) to furnish the heterocycles **54h** and **54i** in 81-85% yield (entries 8 and 9). The quinolyl organometallic **53i** readily underwent a copper-catalyzed allylation reaction (5 mol% CuCN·2LiCl) with 3-bromocyclohex-1-ene (**57i**; 0.9 equiv) to give the functionalized quinoline **54j** in 76% yield (entry 10). Furthermore, the zinc reagent **53i** was subjected to Pd-catalyzed cross-couplings (5 mol% of PEPPSI-IPr) with the (hetero)aryl iodides **57j-l** (0.9 equiv) to afford **54k-m** in 48-70% yield (Table 7, entries 11-13). Moreover, reaction with *S*-(3,4-dichlorophenyl) benzenesulfonothioate (**57m**; 0.9 equiv) and Cu-mediated acylation with the acyl chlorides **57n-q** (0.8-0.9 equiv) furnished the substituted heteroarenes **54n-r** in 55-67% yield (entries 14-18).

[198] a) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749. b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed*. **2007**, *46*, 2768. c) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443.

Table 7: Reaction of heteroarylmethylzinc reagents of type **53** with electrophiles of type **57** to afford products of type **54**.

Entry	Zinc Reagent	Electrophile	Product, Yield[a]
1	 **53a**	 **57a**	 **54a**: 80%[189]
2	 **53b**	 **57b**	 **54b**: 93%[b],[190]
3	 **53c**	 **57c**	 **54c**: 88%[d],[189]
4	 **53d**	 **57d**	 **54d**: 72%[b],[190]
5	 **53e**	 **57e**	 **54e**: 85%[b],[190]
6	 **53f**	 **57f**	 **54f**: 80%[c],[190]
7	 **53**	 **57f**	 **54g**: 98%[c]
8	 **53g**	 **57g**	 **54h**: 81%

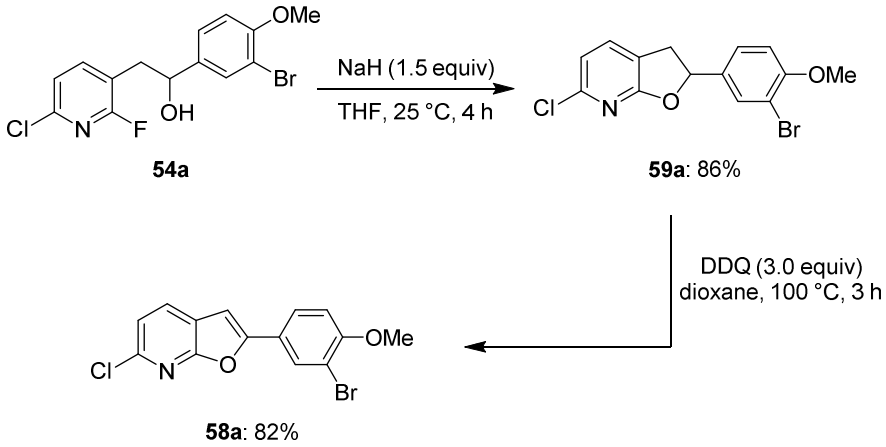
9		**53g**		**57h**		**54i**: 85%
10		**53i**		**57i**		**54j**: 76%[c]
11		**53i**		**57j**		**54k**: 70%[b]
12		**53i**		**57k**		**54l**: 48%[b]
13		**53i**		**57l**		**54m**: 49%[b]
14		**53i**		**57m**		**54n**: 65%
15		**53i**		**57n**		**54o**: 66%[d]
16		**53i**		**57o**		**54p**: 67%[d]
17		**53i**		**57p**		**54q**: 62%[d]
						

18	**53i**	**57q**	**54r**: 55%[d]

[a] Yield of isolated, analytically pure product. [b] Obtained by Pd-catalyzed cross-coupling using 1 or 5 mol% PEPPSI-IPr and 0.9 equiv of the aryl halide. [c] Obtained by Cu-catalyzed allylation using 5 mol% CuCN·2LiCl and 0.9 equiv of the allyl bromide. [d] Obtained by Cu-mediated acylation using 1.1 equiv CuCN·2LiCl and 0.8-0.9 equiv of the acyl chloride.

2.4.3 PREPARATION OF HIGHLY FUNCTIONALIZED ANNULATED HETEROCYCLES

Besides for common functionalization reactions such as the ones applied above, the zinc reagents of type **53** proved to be versatile organometallic intermediates for the construction of polyfunctional fused *N*- and *O*-containing heterocycles, and a variety of furopyridines (**58**), which find numerous applications in pharmaceutical chemistry as enzyme inhibitors, receptors and modifiers,[199] was successfully prepared. Thus, the previously prepared heterocyclic alcohol **54a** (Table 7, entry 1) was treated with NaH (1.5 equiv) in THF (25 °C, 4 h) to furnish the dihydrofuropyridine **59a** in 86% yield after cyclization reaction, and subsequent oxidation using DDQ[200] (DDQ = 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone; 3.0 equiv) afforded the fused heterocycle **58a** in 82% yield (Scheme 91).[189]

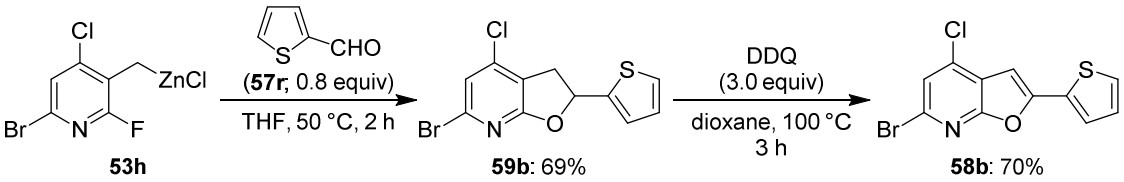


54a **59a**: 86% **58a**: 82%

Scheme 91: Preparation of furopyridine **58a** starting from pyridyl alcohol **54a**.

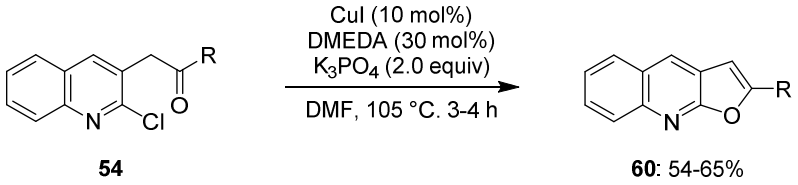
Similarly, the dihydrofuropyridine **59b** was obtained in 69% yield by a thermal cyclization reaction of the previously prepared pyridylzinc reagent **53h** (Table 5, entry 8) with thiophene-2-carbaldehyde (**57r**; 0.8 equiv, 50 °C, 2 h). Subsequent oxidation using DDQ[200] furnished the polyfunctional furopyridine **58b** in 70% yield (Scheme 92).

[199] a) A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, F. Marinelli, *Org. Lett.* **2002**, *4*, 2409. b) B. M. Moore, S. Gurley, S. Mustafa, WO 2011/022679, **2011**. c) J. J. Nunes, M. W. Martin, R. White, D. McGowan, J. E. Bemis, F. Kayser, J. Fu, J. Liu, X. Y. Jiao, US 2006/0046977, **2006**.
[200] E. C. Taylor, J. E. Macor, J. L. Pont, *Tetrahedron* **1987**, *43*, 5145.



Scheme 92: Preparation of furopyridine **58b** starting from pyridylzinc reagent **53h**; additional complexed salts are omitted for sake of clarity.

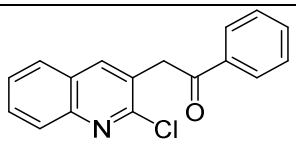
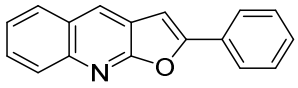
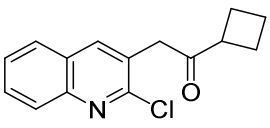
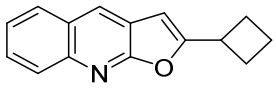
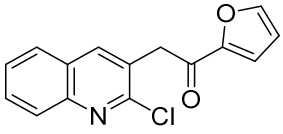
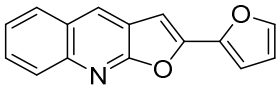
Noteworthy, such fused *N*- and *O*-containing heteroarenes are as well accessible starting from "heterobenzylic" ketones by a copper-catalyzed ring closing reaction recently reported by *Ackermann* (Scheme 93).[201]



Scheme 93: Preparation of furoquinolines of type **60** starting from benzylic ketones of type **54**.

Hence, analogously to *Ackermann*'s method, the previously synthesized quinolyl ketones **54o-q** (Table 7, entries 15-17) were smoothly converted to the furoquinolines **60a-c** in 54-65% yield upon treatment with CuI (10 mol%), K_3PO_4 (2.0 equiv) and *N*,*N*'-dimethylethylenediamine (DMEDA; 30 mol%) in DMF (105 °C, 3-4 h; Table 8).

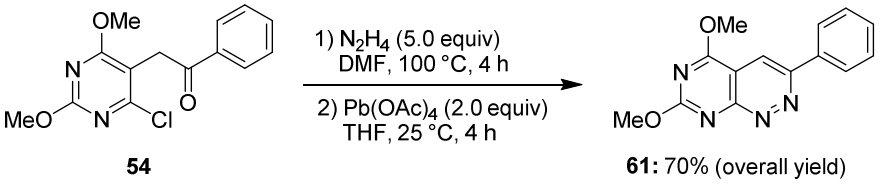
Table 8: Preparation of furoquinolines of type **60**.

Entry	Heterocyclic Chloride	Product (t, Yield[a])
1	 **54o**	 **60a** (4 h, 62%)
2	 **54p**	 **60b** (4 h, 65%)
3	 **54q**	 **60c** (3 h, 54%)

[a] Yield of isolated, analytically pure product.

[201] L. Ackermann, L. T. Kaspar, *J. Org. Chem.* **2007**, 72, 6149.

Also tetraazanaphthalenes display biorelevant heterocycles. However, the methods for their preparation outlined in the literature are nonstraightfoward.[202] Using our functionalized heteroarylmethyl derivatives, these tetraazanaphthalenes are now readily available. Thus, the previously prepared pyrimidyl ketone **54c** (Table 7, entry 3) was treated with hydrazine (5.0 equiv) in DMF (100 °C, 4 h) to give the tetraazanaphthalene **61** in 70% overall yield after oxidation with $Pb(OAc)_4$[203] (2.0 equiv; Scheme 94).[189]



Scheme 94: Preparation of tetraazanaphthalene **61** starting from pyrimidyl ketone **54c**.

2.4.4 APPLICATION TO THE SYNTHESIS OF A BIOLOGICALLY ACTIVE COMPOUND

As mentioned before, the furopyridyl motif is of key importance in pharmaceutical chemistry, and great interest relies on this substance class with regard to cycotoxical studies.[199] In this context, especially the CB1 modifier **62**[199b] and the Lck and ACK-1 enyzme inhibitor **62**[199b] have attracted a lot of attention (Figure 4).

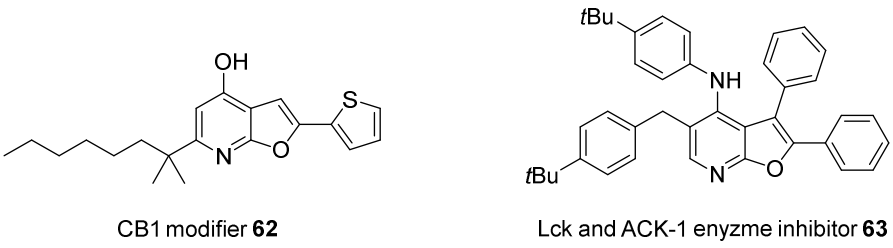
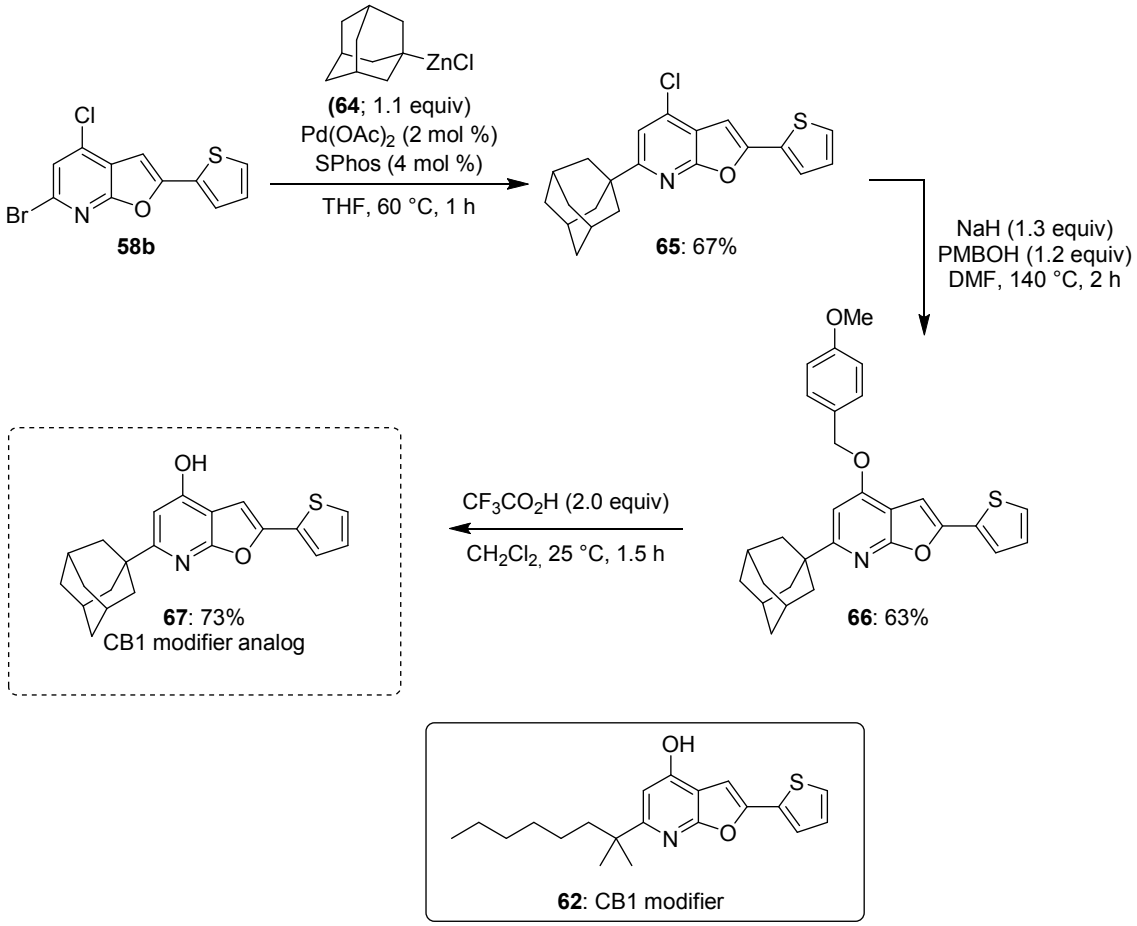


Figure 4: Bioactive CB1 modifier **62** and Lck and ACK-1 enyzme inhibitor **63**.

Therefore, we envisioned to apply our strategy to the synthesis of an anlogue of the CB1 modifier **62**. To this end, we decided to modify the structure of **62** in that manner that the 1,1-dimethylheptyl group was replaced by the highly lipophilic adamantyl group, which displays an essential motif in medicinal chemistry.[204] Thus, the previously prepared fused heterocycle **58b** (Scheme 92) was subjected to a Pd-catalyzed *Negishi* cross-coupling[176] (2 mol% $Pd(OAc)_2$, 4 mol% SPhos[205]) with the adamantylzinc reagent

[202] a) W. R. Mallory, R. W. Morrison, *J. Org. Chem*. **1980**, *45*, 3919. b) V. L. Styles, R. W. Morrison Jr., *J. Org. Chem*. **1985**, *50*, 346.
[203] J. K. Kochi, *Org. React*. **1972**, *19*, 279.
[204] For a review on the application of adamantane derivatives in medicinal chemistry, see: L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.* **2013**, *113*, 3516.
[205] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.

64[206] (1.1 equiv, THF, 60 °C, 1 h) to furnish **65** in 67% yield. Subsequent treatment with sodium (*p*-methoxyphenyl)methanolate (PMBO-Na)[207] afforded the alkoxy-heterocycle **66** in 63% yield. Finally, after deprotection of the PMB (*p*-methoxybenzyl)-group with trifluoroacetic acid[208] the CB1 modifier analogue **67** was obtained in 73% yield (Scheme 95).



Scheme 95: Synthesis of the CB1 modifier analogue **67** starting from the previously prepared polyfunctional heterocycle **58b**; additional complexed salts are omitted for sake of clarity.

[206] For the preparation of the adamantylzinc reagent **64**, see: C. Sämann, V. Dhayalan, P. R. Schreiner, P. Knochel, *Org. Lett.* **2014**, *16*, 2418.
[207] For the preparation of PMBO-Na, see: a) P. C. Claude, F.-R. Alexandre, T. Convard, D. Surleraux, WO 2012/109398, 2012. b) J. M. Berge, P. Brown, J. S. Elder, A. K. Forrest, D. W. Hamprecht, R. L. Jarvest, D. J. McNair, R. J. Sheppard, WO 99/55677, **1999**.
[208] For the depotection of PMB-groups, see: M. Llinas-Brunet, J. Bordeleau, C. Godbout, M. Leblanc, B. Moreau, J. O'Meara, WO 2011/063502, **2011**.

3. NEW *IN SITU* METALATIONS OF FUNCTIONALIZED ARENES AND HETEROCYCLES WITH TMPLI IN THE PRESENCE OF $ZnCl_2$ AND OTHER METAL SALTS

3.1 INTRODUCTION

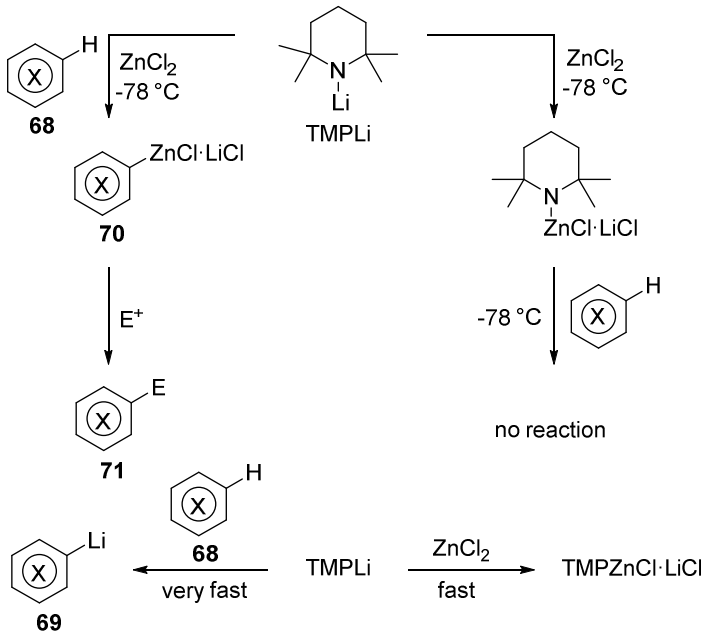
Functionalization of arenes and heteroarenes *via* lithiation displays a versatile tool in organic synthesis and has found numerous applications in pharmaceutical, agrochemical and material science.[29,209] In this context, especially TMPLi[146] as a strong base has attracted a lot of attention when it comes to metalation of rather unactivated (hetero)arenes. However, due to the high reactivity of TMPLi, the functional group tolerance of this base is limited, precluding the efficient metalation of sensitive substrates functionalized with ester, cyano or nitro groups. To this end, a wide range of chemoselective and less reactive amide bases has been prepared,[210] including the LiCl-complexed magnesium bases TMPMgCl·LiCl[44] and TMP_2Mg·2LiCl,[45] as well as the zinc-derived amides TMPZnCl·LiCl[64] and TMP_2Zn·2LiCl[46,65] and the scope of some of these bases could further be extended by the use of Lewis acids such as BF_3·OEt_2.[163] To overcome the rather limited functional group compatibility of lithium organyls generated by TMPLi, metalation reactions using this base were often conducted in the presence of electrophiles (Barbier *in situ* trapping).[164,165]

During our studies with various *N*-heterocycles, we often encountered heteroarenes which, on the one hand, could not efficiently be metalated with magnesium bases such as TMPMgCl·LiCl and TMP_2Mg·2LiCl, but, on the other hand, readily decomposed at -78 °C within a few minutes or immediately after addition of the stronger lithium bases TMPLi and LDA.[105] Having the above mentioned *in situ* trapping methods in mind, we therefore envisioned the deprotonation of (hetero)arenes **68** using TMPLi in the presence of metal salts such as $ZnCl_2$, $MgCl_2$, CuCN and $LaCl_3$ giving a practical access to the corresponding Zn-, Mg-, Cu- and La-organometallics. Thus, when mixing substrates **68** with the metal salts, subsequent treatment with TMPLi (-78 °C, 5 min) should first lead to a kinetic lithiation and then, to transmetalation of the thus prepared lithium reagents **69** with the metal salt present in the reaction mixture, resulting in a thermodynamically more

[209] a) J. Clayden, *Organolithiums: Selectivity for Synthesis*, (Elsevier Science Ltd., Oxford, UK), **2002**. b) M. Schlosser, *Organometallics in Synthesis*, 3rd ed. (Ed.: M. Schlosser), Wiley, New York, **2013**, Chapter 1. c) *Fieser and Fieser`s reagents for organic synthesis*, Wiley, Hoboken, **2011**, and earlier volumes. d) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470. e) C. Unkelbach, D. F. O`Shea, C. Strohmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 553. f) A. Salomone, F. M. Perna, A. Falcicchio, S. O. Nilsson Lill, A. Moliterni, R. Michel, S. Florio, D. Stalke, V. Capriati, *Chem. Sci.* **2014**, *5*, 528.

[210] a) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. b) A. Harrison-Marchand, F. Mongin, *Chem. Rev.* **2013**, *113*, 7470. c) E. Crosbie, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Dalton Trans.* **2012**, *41*, 1832. d) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539. e) F. Mongin, A. Bucher, J.P. Bazureau, O. Bayh, H. Awad, F. Trécourt, *Tetrahedron Lett.* **2005**, *46*, 7989.

stable organometallic (**70**), which readily reacts with electrophiles to furnish the appropriate products of type **71**. For a successful realization of this lithiation-transmetalation method, it has to be provided that the reaction between TMPLi and the (hetero)arene **68** is faster than the transmetalation of TMPLi with the metal salt present. In this context, it should be noticed that substrates of type **68** are unreactive towards metalation with TMPZnCl·LiCl at -78 °C (Scheme 96).



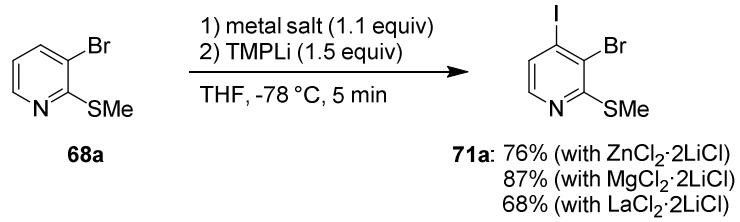
Scheme 96: Reaction of a mixture of $ZnCl_2$ and aromatic or heterocyclic substrate **68** with TMPLi at -78 °C leading to zinc reagents of type **70** *via* a lithiation-transmetalation sequence; X = N, CH.

3.2 METALATION OF SENSITIVE FUNCTIONALIZED HETEROARENES USING TMPLI IN THE PRESENCE OF METAL SALTS

As mentioned before, during our studies we were often faced with *N*-heterocycles, mainly pyridines, which were difficult to functionalize by direct metalation using amide bases. In this regard, the metalation with amides such as TMPMgCl·LiCl,[44] $TMP_2Mg·2LiCl$[45] or $TMP_2Zn·2MgCl_2·2LiCl$[65] proved to be insufficient with respect to the conversion of the metalation process, or the time that was necessary to reach a consumption of the starting material above 60%. In contrast to this, treatment of these substrates at -78 °C with lithium derived bases such as TMPLi[146] and LDA[105] mostly resulted in decomposition of the heteroarenes either directly after the addition of the base or within 5 min at the indicated temperature. With our lithiation-transmetalation strategy in hand, these problems could successfully be overcome. When mixing the heteroarene with a metal salt ($ZnCl_2$, $MgCl_2$, CuCN or $LaCl_3$) and treating it with TMPLi, the

heteroarene was indeed first lithiated to generate a rather unstable kinetic intermediate, but instead of decomposing, these reactive organometallics were readily transmetalated with the metal salt present in the reaction mixture to form the corresponding Zn-, Mg-, Cu-or La-reagents showing an excellent thermal stability.

The metalation of thiomethyl-substituted pyridine **68a**[211] for example, proved to be quite challenging. While no conversion could be detected *via* GC when **68a** was subjected to deprotonation with TMPMgCl·LiCl (0 °C, 1 h) or with the frustrated Lewis pair TMPMgCl·LiCl/BF_3·OEt_2 (-40 °C to 0 °C, 4 h), treatment with TMPLi at -78 °C for 5 min gave full consumption of the starting material, but 91% decomposition. Similarly, using TMP_2Mg·2LiCl at -20 °C for 1.5 h led to 70% conversion, but 38% decomposition. In contrast to this, the pyridine **68a** was readily metalated with TMPLi (1.5 equiv) in the presence of $ZnCl_2$·2LiCl, $MgCl_2$·2LiCl or $LaCl_3$·2LiCl (1.1 equiv) to give, after iodolysis, the iodide **71a** in 68-87% yield (Scheme 97).[212]



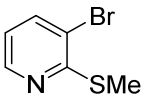
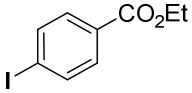
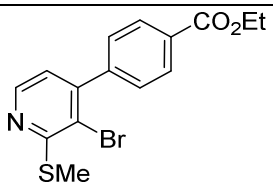
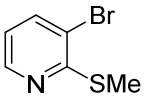
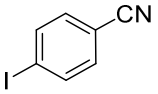
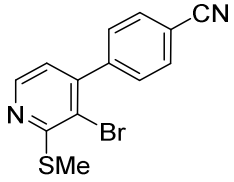
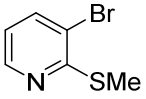
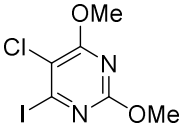
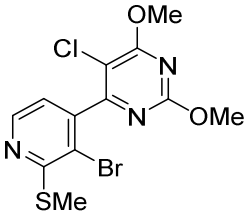
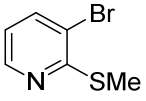
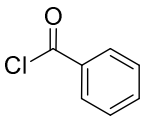
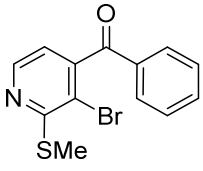
Scheme 97: Metalation of pyridine **68a** using TMPLi in the presence of $ZnCl_2$·2LiCl, $MgCl_2$·2LiCl or $LaCl_3$·2LiCl.

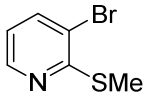
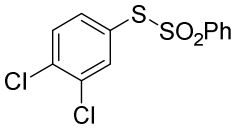
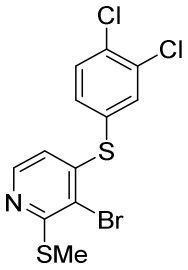
Besides iodolysis, other reactions such as *Negishi* cross-couplings,[176] *Negishi* acylations[213] and addition reactions to *S*-benzenesulfonothioates were successfully conducted to produce the corresponding pyridines **71b-f** (Table 9). Thus, when pyridine **68a** was subjected to metalation with TMPLi (1.5 equiv) in the presence of $ZnCl_2$·2LiCl (1.1 equiv), the resulting zinc reagent readily reacted in a Pd-catalyzed cross-coupling (3 mol% $Pd(dba)_2$, 6 mol% P(2-furyl)$_3$) with 0.9 equiv of ethyl 4-iodobenzoate (**72a**) to give the highly functionalized pyridine **71b** in 80% yield (Table 9, entry 1). Similarly, *Negishi* cross-coupling[176] with the aryl iodide **72b** produced the heterocycle **71c** in 62% yield, while coupling with the sterically demanding iodo heteroarene **72c** (0.9 equiv) furnished the desired product **71d** with only a moderate yield of 39% attributed to the bulkiness of the electrophile (entries 2 and 3). Noteworthy, initial attempts to perform acylation reactions with the pyridine **68a** were less successful. Since an *in situ* quenching

[211] For details on the preparation of this substrate, please refer to: C. Experimental Section.
[212] The complexation of the metal salts by LiCl enhances the solubility and often increases the reaction yields by ca. 10-20%.
[213] E.-i- Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

with CuCN·2LiCl only led to decomposition of the pyridine **68a**, for acylations reactions other strategies had to be performed. Thus, when the zinc reagent derived from **68a** was transmetalated with CuCN·2LiCl[160] (1.5 equiv) and reacted with benzoyl chloride (**72d**; 0.9 equiv), the resulting ketone **71e** was obtained in 22% yield (entry 4). An improvement could be achieved when **68a** was treated with TMPLi in the presence of $LaCl_3$·2LiCl (1.1 equiv) to form a lanthanium intermediate which was subsequently acylated with **72d** furnishing the ketone **71e** in 30% yield (entry 5). However, best results were obtained metalating **68a** with TMPLi/$ZnCl_2$·2LiCl and performing a *Negishi* acylation[213] using 2 mol% $Pd(PPh_3)_4$ to afford the desired aroylated pyridine **71e** in 56% yield (entry 6). Finally, **68a** was successfully treated with TMPLi/$MgCl_2$·2LiCl to give the thioether **71f** in 60% yield after reaction with *S*-(3,4-dichlorophenyl) benzenesulfonothioate[197] (**72e**; 0.9 equiv; entry 7).

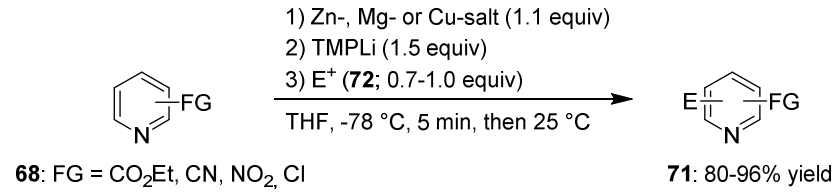
Table 9: Reaction of pyridine **68a** with TMPLi in the presence of $ZnCl_2$·2LiCl or $MgCl_2$·2LiCl and subsequent functionalization with electrophiles of type **72**.

Entry	Substrate	Electrophile	Product, Yield[a]
1	 **68a**	 **72a**	 **71b**: 80%[b][d]
2	 **68a**	 **72b**	 **71c**: 62%[b][d]
3	 **68a**	 **72c**	 **71d**: 39%[b][d]
4	 **68a**	 **72d**	 **71e**: 22%[b][e]
5			**71e**: 30%[f]

6			**71e**: 56%[b][g]
			
7	**68a**	**72e**	**71f**: 60%[c]

[a] Yield of isolated, analytically pure product. [b] $ZnCl_2 \cdot 2LiCl$ was added. [c] $MgCl_2 \cdot 2LiCl$ was added. [d] Obtained by a Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$, 6 mol% P(2-furyl)$_3$ and 0.9 equiv of aryl iodide. [e] Otbained by a Cu-mediated acylation using 1.5 equiv of $CuCN \cdot 2LiCl$ and 0.9 equiv of acyl chloride. [f] $LaCl_3 \cdot 2LiCl$ was added. [g] Obtained by a Pd-catalyzed acylation using 2 mol% $Pd(PPh_3)_4$ and 0.9 equiv of acyl chloride.

Worth mentioning, this lithiation/transmetalation strategy could be extended to other functionalized pyridines (**68b**, **68c** and **68d**) bearing sensitive groups such as cyano-, ester- and nitro-substituents. No attack of TMPLi or the generated lithium intermediates onto these elctrophilic moieties was observed, leaving the heterocycles intact. Although some of these heteroarenes may be metalated in a different manner,[214,215,216] our strategy displays a simple preparative alternative, which directly delivers the appropriate organometallics within 5 min. In this context, besides Zn- and Mg- salts, also $CuCN \cdot 2LiCl$ could successfully be employed in this method, giving, among others, a direct access to acylated and allylated derivatives (Scheme 98 and Table 10).



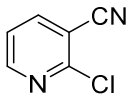
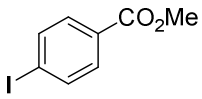
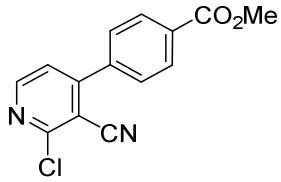
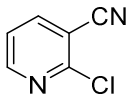
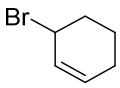
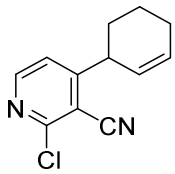
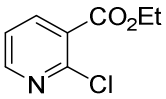
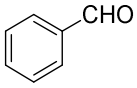
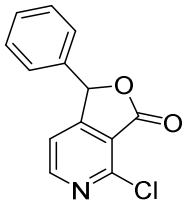
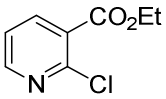
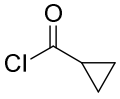
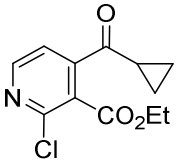
Scheme 98: Metalation of pyridines **68** using TMPLi in the presence of Zn-, Mg- or Cu-salts and subsequent functionalization with electrophiles.

In this fashion, cyanopyridine **68b** was metalated with TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$ to furnish the arylated product **71g** in 90% yield after Pd-catalyzed cross-coupling (Table 10, entry 1).[217] The concomitant use of TMPLi and $CuCN \cdot 2LiCl$

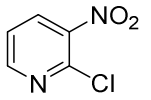
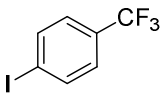
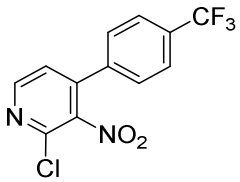
[214] For **68b**, an alternative metalation with $TMP_2Mn \cdot 2MgCl \cdot 4LiCl$ at 0 °C within 45 min is possible, see: S. H Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[215] For **68c**, an alternative metalation with $TMP_2Zn \cdot 2MgCl_2$ 2LiCl at 25 °C within 5 h is possible, see: reference 65a.
[216] For **68d**, an alternative metalation with $TMP_2Zn \cdot 2MgCl_2$ 2LiCl at -40 °C within 1.5 h is possible, see: reference 65a.

successfully converted **68b** to a copper species, and subsequent allylation with 3-bromocyclohex-1-ene (**72g**; 1.0 equiv) afforded the pyridine **71h** in 96% yield (entry 2).[217] Also, ethyl 2-chloronicotinate (**68c**) was subjected to TMPLi/$MgCl_2$ and TMPLi/CuCN·2LiCl to give the expected products **71i-j** in 94% yield each after reaction with the electrophiles **72h** (1.0 equiv) and **72i** (0.8 equiv; entries 3 and 4).[218] Similarly, the nitropyridine **68d** was readily metalated using TMPLi in the presence of $ZnCl_2$·2LiCl. After *Negishi* cross-coupling with 1-iodo-4-(trifluoromethyl)benzene (**72j**; 0.7equiv), the appropriate heterocycle **71k** was obtained in 80% yield (entry 5).[217]

Table 10: Reaction of pyridines **68** with TMPLi in the presence of $ZnCl_2$, $MgCl_2$ or CuCN and subsequent functionalization with electrophiles of type **72**.

Entry	Substrate	Electrophile	Product, Yield[a]
1	 **68b**	 **72f**	 **71g**: 90%[b][e][217]
2	 **68b**	 **72g**	 **71h**: 96%[c][217]
3	 **68c**	 **72h**	 **71i**: 94%[d][218]
4	 **68c**	 **72i**	 **71j**: 94%[c][218]

[217] These experiments were conducted by A. Frischmuth and are given here for sake of completeness. For further experimental details, see: Ph.D. thesis Annette Frischmuth, LMU Munich, **2014**.
[218] These experiments were conducted by M. Fernández and are given here for sake of completeness.

			
5	**68d**	**72j**	**71k**: 80%[b][e][217]

[a] Yield of isolated, analytically pure product. [b] $ZnCl_2 \cdot 2LiCl$ was added. [c] $CuCN \cdot 2LiCl$ was added. [d] $MgCl_2$ was added. [e] Obtained by a Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$, 4 mol% P(2-furyl)$_3$ and 0.9 equiv of aryl iodide.

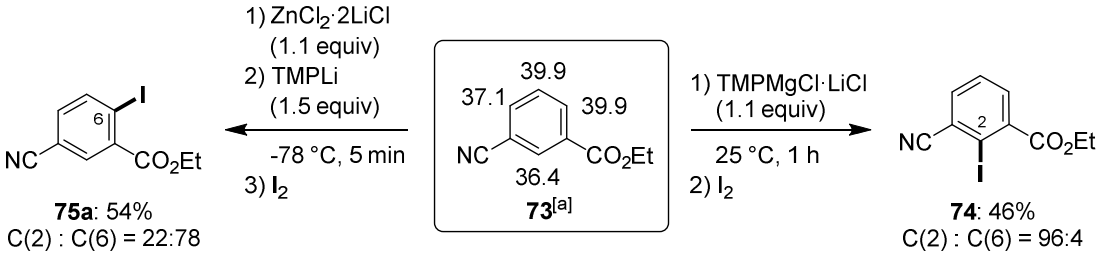
3.3 UNPRECEDENTED REGIOSELECTIVITIES IN THE METALATION OF (HETERO)ARENES USING TMPLI IN THE PRESENCE OF METAL SALTS

Among our observations regarding sensitive aromatics such as the ones mentioned before, during our studies, we came across another even more important characteristic of this *in situ* trapping method. For example, the metalation of ethyl 3-cyanobenzoate (**73**)[211] with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.55 equiv) takes 30 h at 25 °C,[65b] and we therefore envisioned to subject this sensitive arene to our fast and direct lithiation/transmetalation strategy. To this end, we tested different metal salts in combination with TMPLi and found the system $TMPLi/ZnCl_2 \cdot 2LiCl$ to give the best results. However, the outcome of this metalation strategy was surprising.

The calculated pK_a values[219] for the different positions of ethyl 3-cyanobenzoate (**73**) indicate H(2) to be the most acidic proton. Thus, metalation with $TMPMgCl \cdot LiCl$ led, after iodolysis, to the thermodynamically more stable iodide **74** in 46% (position 2 : position 6 = 96:4; Scheme 99). In contrast, due to the kinetic nature of TMPLi, treatment of **73** with this base in the presence of $ZnCl_2 \cdot 2LiCl$ allowed a lithiation in the sterically less hindered position 6 with a calculated pKa value ca. 10^4 times more basic than H(2) and adjacent to the most powerful directing group,[29] the ethyl ester moiety. Usually, this ring position is notoriously difficult to metalate. However, metalation of **73** was complete after 5 min at -78 °C and afforded, after iodolysis, the corresponding iodide **75a** accompanied by ca. 15% of the iodide **74**, which was easily separated by column chromatography to furnish the pure aryl iodide **75a** in 54% yield and with a good regioselectivity (position 2 : position 6 = 22:78; Scheme 99). Noteworthy, independently

[219] The calculations for the C-H acidities have been conducted by F. Achrainer following the protocol proposed by *Guo* and coworkers, see: K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568. For more details, see: A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/anie.201403688.

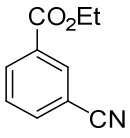
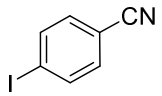
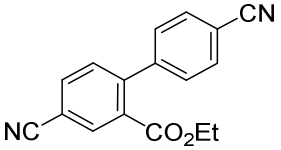
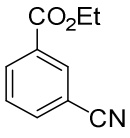
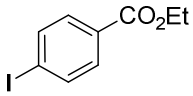
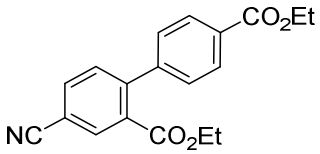
generated "$(TMP)_3ZnLi \cdot 2LiCl$"[220] metalates **73** with a decreased regioselectivity of 44:56 (C(2):C(6)) and only a low conversion after 5 min at -78 °C.



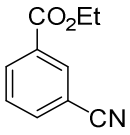
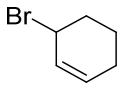
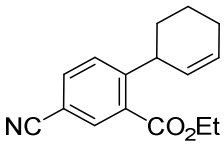
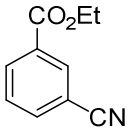
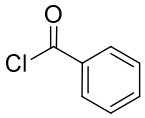
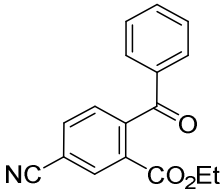
Scheme 99: Regioselectivity switch in the metalation of ethyl 3-cyanobenzoate (**73**) by TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$ or by TMPMgCl·LiCl. [a] Calculated pK_a values for H(2), H(4), H(5) and H(6).

Yet, using TMPLi and $ZnCl_2 \cdot 2LiCl$ gives access to a zinc reagent which was subjected to further functionalizations in position 6 furnishing, after *Negishi* cross-coupling with aryl iodides **72b** and **72a**, the corresponding 6-arylated derivatives **75b-c** in 84-87% yield and with a crude regioselectivity of 86:14 and 88:12, respectively (Table 11, entries 1 and 2). Similarly, a copper-mediated allylation and acylation[160] was performed with the generated zinc intermediate to afford the 6-functionalized arenes **75d** and **75e** in 50-79% yield (entries 3 and 4).

Table 11: Reaction of arene **73** with TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$ and subsequent functionalization with electrophiles of type **72**.

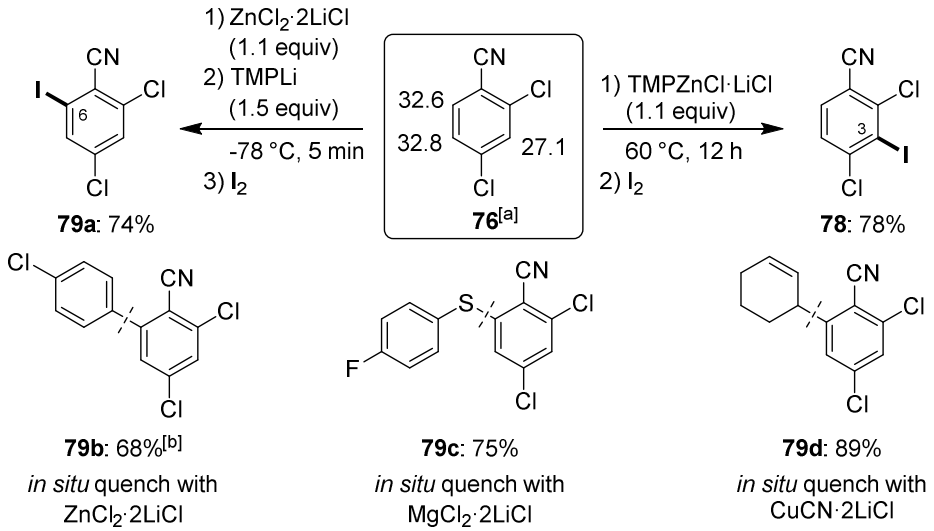
Entry	Substrate	Electrophile	Product (T, t, Yield[a])	Regioselectivity (C(6):C(2))
1	 **73**	 **72b**	 **75b** (25 °C, 4 h, 84%)[b][c]	86:14
2	 **73**	 **72a**	 **75c** (25 °C, 4 h, 87%)[b][c]	88:12

[220] a) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, *72*, 6602. b) J.-M. L`Helgoual`ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama, F. Mongin, *J. Org. Chem.* **2008**, *73*, 177. c) K. Snégaroff, S. Komagawa, F. Chevallier, P. C. Gros, S. Golhen, T. Roisnel, M. Uchiyama, F. Mongin, *Chem. Eur. J.* **2010**, *16*, 8191. d) F. Chevallier, Y. S. Halauko, C. Pecceu, I. F. Nassar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Mongin, *Org. Biomol. Chem.* **2011**, *9*, 4671. e) P. Garcia-Alvarez, R. E. Mulvey, J. A. Parkinson, *Angew. Chem. Int. Ed.* **2011**, *50*, 9668.

3	 **73**	 **72g**	 **75d** (-40 °C, 4 h, 79%)[b][d]	80:20
4	 **73**	 **72d**	 **75e** (25 °C, 16 h, 50%)[b][e]	85:15

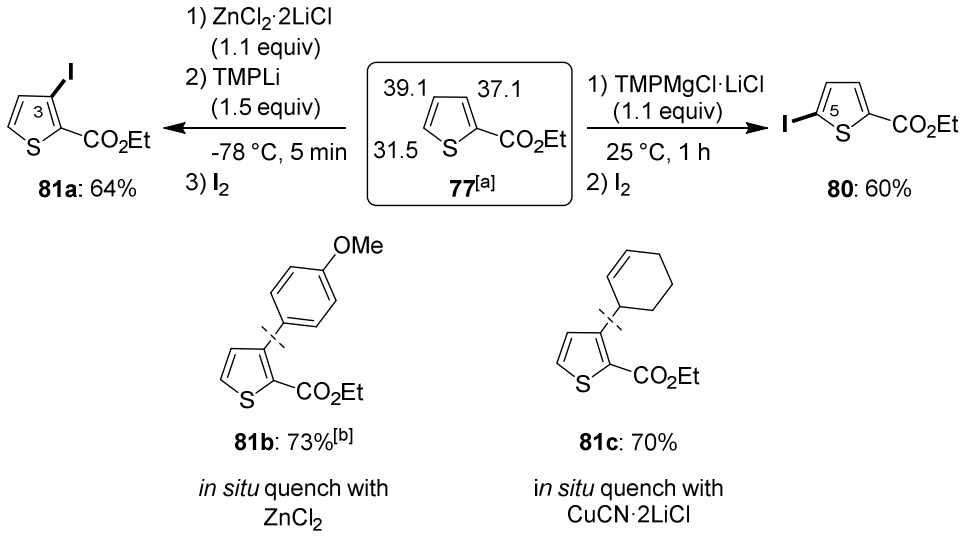
[a] Yield of isolated, analytically pure product. [b] $ZnCl_2 \cdot 2LiCl$ was added. [c] Obtained by a Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$, 6 mol% $P(2\text{-furyl})_3$ and 0.7 equiv of aryl iodide. [d] Otbained by a Cu-mediated allylation using 1.5 equiv of $CuCN \cdot 2LiCl$ and 0.7 equiv of acyl chloride. [e] Otbained by a Cu-mediated acylation using 1.5 equiv of $CuCN \cdot 2LiCl$ and 0.7 equiv of acyl chloride.

Analogous regioselectivity switches were also observed for 2,4-dichlorobenzonitrile (**76**) and ethyl thiophene-2-carboxylate (**77**).[217] When **76** was treated with TMPZnCl·LiCl at 60 °C for 1 h, subsequent iodolysis furnished the 3-iodo derivative **78** in 78% yield due to H(3) being the most acidic proton. This regioselectivity in metalation was different to the one obtained upon the concomitant use of TMPLi (1.5 equiv) and $ZnCl_2 \cdot 2LiCl$ (1.1 equiv), which, due to the *ortho*-directing effect of the cyano substituent,[29] occured in position 6, although H(6) is 10^6 times less acidic than H(3). After iodination, the corresponding 6-iodo derivative **79a** was obtained in 74% yield with a regioselectivity of ca. 95:5 (position 6 : position 3; Scheme 100). Accordingly, *Negishi* cross-coupling[176] affords the 6-arylated arene **79b** in 68% yield. This reaction sequence could be extended to the use of the metal salts $MgCl_2 \cdot 2LiCl$ and $CuCN \cdot 2LiCl$[160] producing the desired derivatives **79c** and **79d** in 75-89% yield after reaction with *S*-(4-fluorophenyl) benzenesulfonothioate[197] (**72k**; 0.9 equiv) and 3-bromocyclohex-1-ene (**72g**; 0.9 equiv; Scheme 100).



Scheme 100: Regioselectivity switch in the metalation of 2,4-dichlorobenzonitrile (**76**) by TMPLi in the presence of metal salts or TMPZnCl·LiCl. [a] Calculated pK_a values for H(3), H(5) and H(6). [b] Obtained by a Pd-catalyzed cross-coupling with 2% $[Pd(dba)_2]$ and 4% P(2-furyl)$_3$ at 25 °C in 2 h.

Similar results were obtained for the heterocycle **77**. As calculations of the pK_a values reveal,[219] H(5) is ca 10^6 times more acidic than H(2). Thus, metalation wih TMPMgCl·LiCl[44] readily furnished, after iodolysis, the thermodynamically favored 5-iodinated thiophene **80** in 60% yield. However, due to the *ortho*-directing[29] effect of the ester moiety, metalation with TMPLi in the presence of $ZnCl_2$ occured in position 2, affording the corresponding 2-iodinated compound **81a** in 64% yield (Scheme 101). Accordingly, this metalation process was successfully used for the preparation of the appropriate thienyl derivatives **81b** and **81c** in 70-73% yield (Scheme 101).



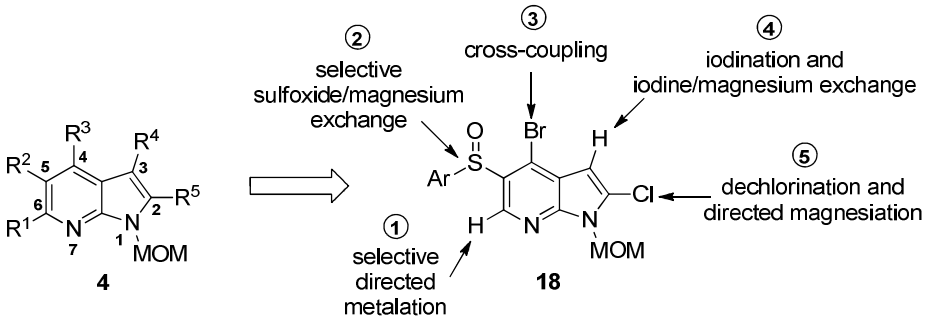
Scheme 101: Regioselectivity switch in the metalation of ethyl thiophen-2-carboxylate (**77**) by TMPLi in the presence of metal salts or TMPMgCl·LiCl. [a] Calculated pKa values for H(3), H(4), and H(5). [b] Obtained by a Pd-catalyzed cross-coupling with 2% $[Pd(dba)_2]$ and 4% P(2-furyl)$_3$ at 25 °C in 0.5 h.

7. SUMMARY AND OUTLOOK

The first part of this work focused on the development of a convenient and general regioselective functionalization of all ring positions of the 7-azaindole scaffold. To this end, starting from simple 2-amino-5-bromopyridine an appropriately substituted azaindole precursor was prepared which allowed us to functionalize the 7-azaindole ring in a predictable manner using a combination of directed metalation, halogen/magnesium and sulfoxide/magnesium exchange. Furthermore, the general preparation of various heteroarylmethylzinc reagents by LiCl-promoted zinc insertion into the corresponding chloromethyl heteroarenes, along with a facile and straightforward synthesis of these chloromethyl precursors displayed a major part in this work. The obtained zinc compounds were subjected to Pd-catalyzed cross-couplings, Cu-mediated acylations, Cu-catalyzed allylations and addition reactions to aldehydes. In addition, they proved to be versatile intermediates for the construction of fused *N*- and *O*-heterocycles and gave access to an analogue of a reported CB1 modifier. Finally, a lithiation/transmetalation strategy for the metalation of sensitive functionalized arenes and heteroarenes was developed, using the strong amide base TMPLi in the presence of metal salts such as $ZnCl_2$, $MgCl_2$, CuCN and $LaCl_3$. This *in situ* trapping method not only allowed the metalation and functionalization of sensitive heteroarenes, but also provided metalated intermediates with a different regioselectivity to the one produced with moderately powerful bases such as TMPZnCl·LiCl or TMPMgCl·LiCl, giving access to higly functionalized organometallics difficult to prepare otherwise.

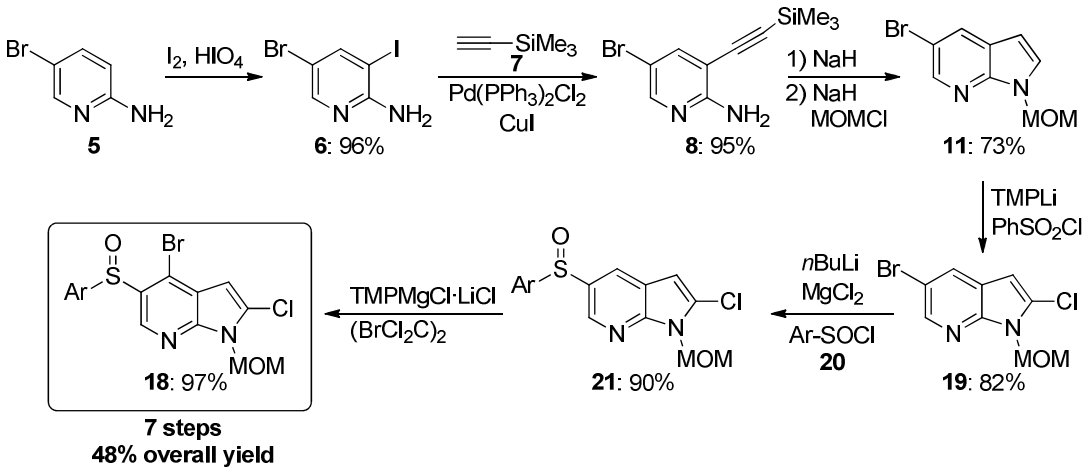
7.1 SYNTHESIS AND FULL-FUNCTIONALIZATION OF THE 7-AZAINDOLE SCAFFOLD VIA SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

In our search for a general and regioselective method for the full functionalization of the 7-azaindole scaffold, we decided to prepare an appropriately substituted 7-azaindole precursor **18**, which bears hidden organometallic pathways giving access to fully functionalized 7-azaindoles of type **4**. Thus, this 7-azaindole derivative **18** allowed us to use a combination of directed magnesiations and lithiations with TMPMgCl·LiCl and TMPLi, as well as halogen/magnesium and sulfoxide/magnesium exchange by means of *i*PrMgCl·LiCl (Scheme 102).



Scheme 102: Key 7-azaindole **18** allowing the preparation of fully substituted 7-azaindoles of type **4**; Ar = 4-methoxy-3,5-dimethyl-phenyl.

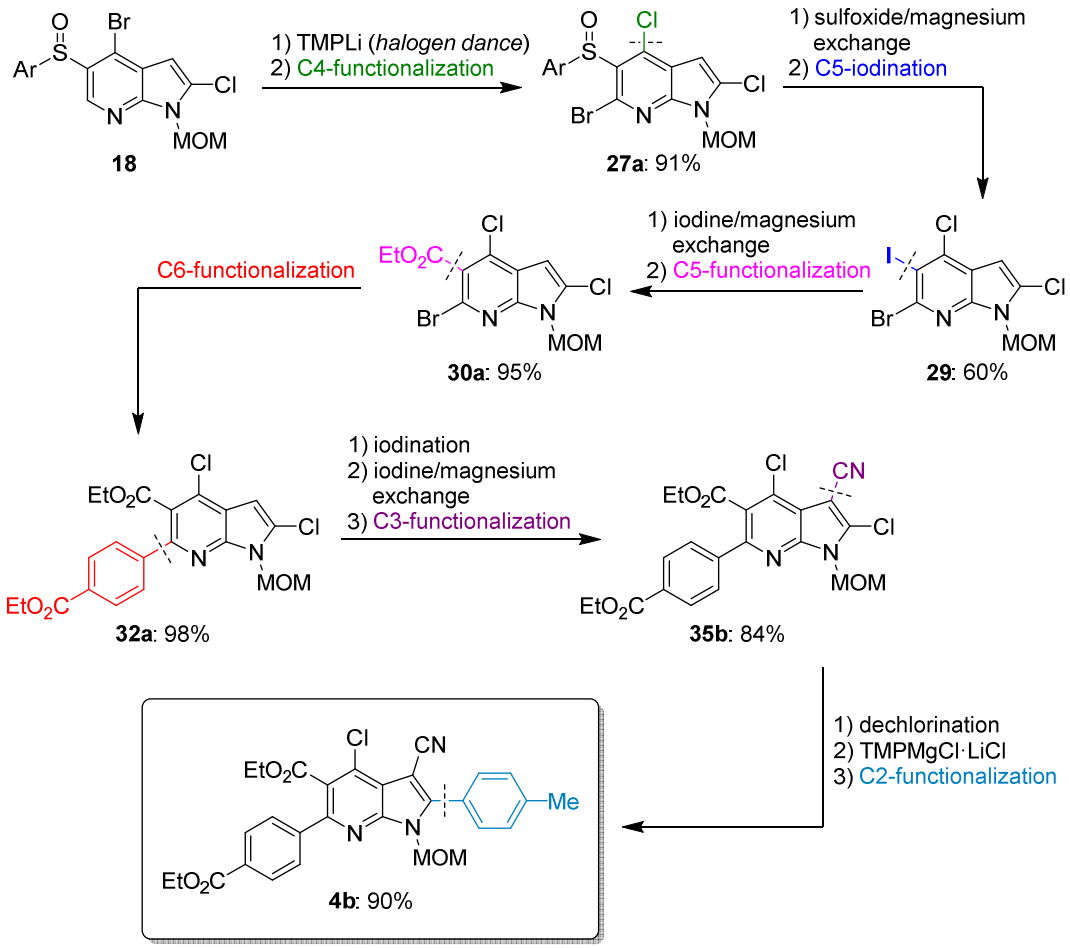
Thereby, the key precursor **18** was prepared in 7 steps in an overall yield of 48% from commercially available 2-amino-5-bromopyridine (**5**; Scheme 103).



Scheme 103: Synthesis of the key 7-azaindole **18** from 2-amino-5-bromopyridine (**5**).

With our new functionalization strategy, various reactions could be performed including cross-couplings, acylations and allylations as well as addition reactions to *S*-benzenesulfonothioates, readily furnishing a wide range of polysubstituted 7-azaindoles in excellent yields and in a general manner. In Scheme 104, an exemplary route to the full-functionalized 7-azaindole **4b** is displayed.

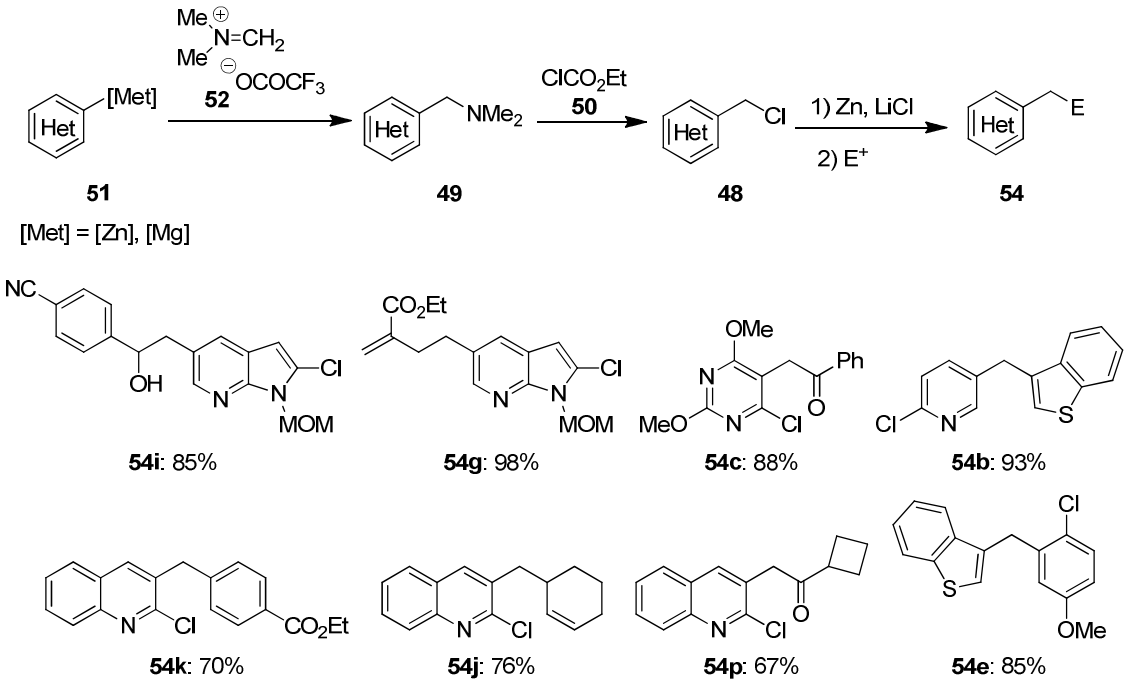
Since highly functionalized 7-azaindoles are of key importance in pharmaceutical chemistry and material science, this method carries great potential allowing to functionalize the 7-azaindole backbone stepwise in a predictable, convenient and general manner and furnishing polyfunctional 7-azaindole derivatives in very good yields.



Scheme 104: Full Functionalization of the 7-azaindole scaffold; Ar = 4-methoxy-3,5-dimethyl-phenyl.

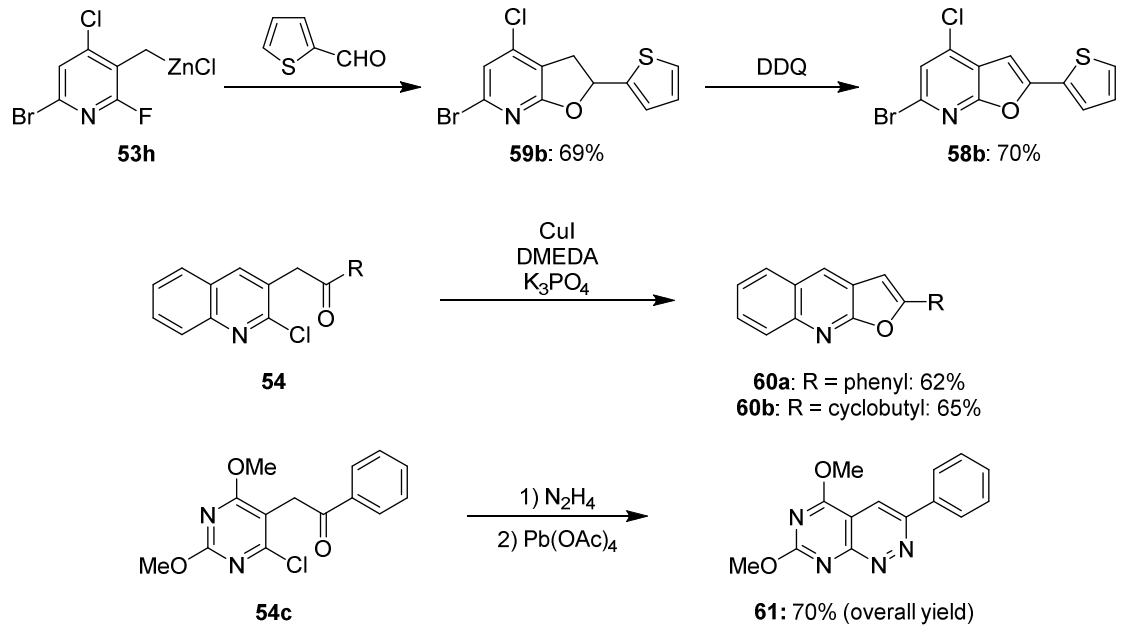
7.2 PREPARATION AND REACTIONS OF HETEROARYLMETHYLZINC REAGENTS

Highly functionalized zinc reagents are an important class of organometallics for organic synthesis. We therefore envisioned the development of a method for the general preparation of heterocyclic benzylic zinc reagents **53** starting from the corresponding heterocyclic chloromethyl precursors **48**, along with a facile and convenient approach to these heterocyclic chlorides (**48**). Thus, readily available heteroaryl organometallics (**51**) were transformed into the corresponding (dimethylamino)methyl derivatives (**49**) to give the appropriate "heterobenzyl" chlorides (**48**) after chlorination of the amino group. Then, these chloromethyl derivatives were subjected to LiCl-promoted direct zinc insertion to furnish various heteroaromatic zinc compounds, which reacted with a wide range of electrophiles in cross-couplings, allylations, acylations and addition reactions to aldehydes and *S*-benzenesulfonothioates. Some examples for the thus-obtained polyfunctional heterocycles **54** are given in Scheme 105.



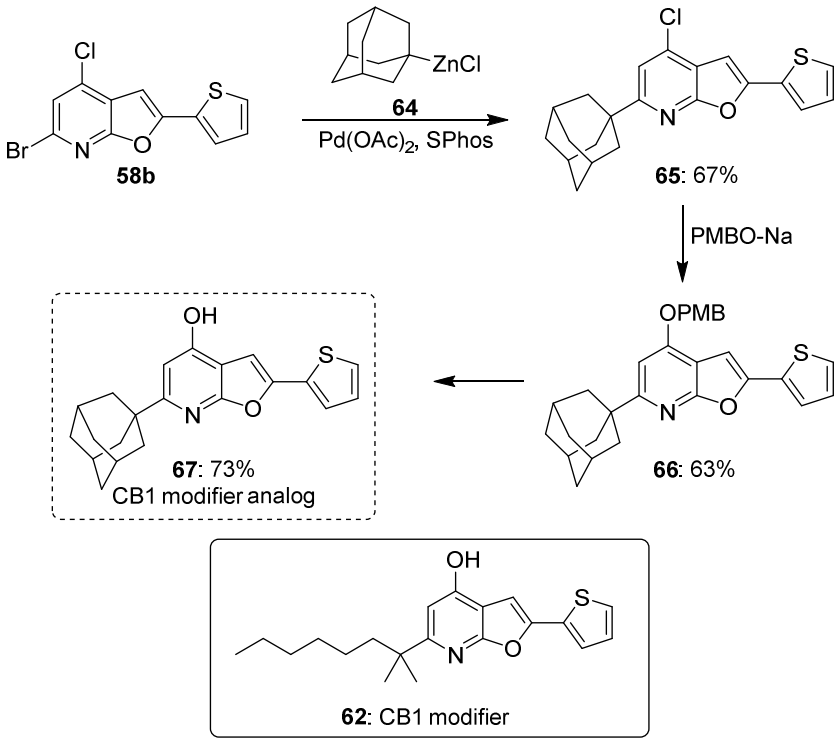
Scheme 105: Preparation of chloromethyl heterocycles of type **48**, their conversion to zinc reagents of type **53**, and subsequent functionalizations leading to products of type **54**.

Moreover, these heteroarylmethylzinc reagents proved to be versatile tools for the preparation of fused *N*- and *O*-heterocycles, and hence, gave a short access to furopyridines, furoquinolines as well as tetraazanaphthalenes (Scheme 106).



Scheme 106: Preparation of fused *N*- and *O*-heterocycles of type **58**, **60** and **61**; additional complexed salts are omitted for sake of clarity.

Furthermore, starting from the previously prepared furopyridine **58b** (Scheme 106), our methodology allowed us to prepare the annulated heterocycle **67**, which displays an analogue of a reported CB1 modifier (**62**; Scheme 107).

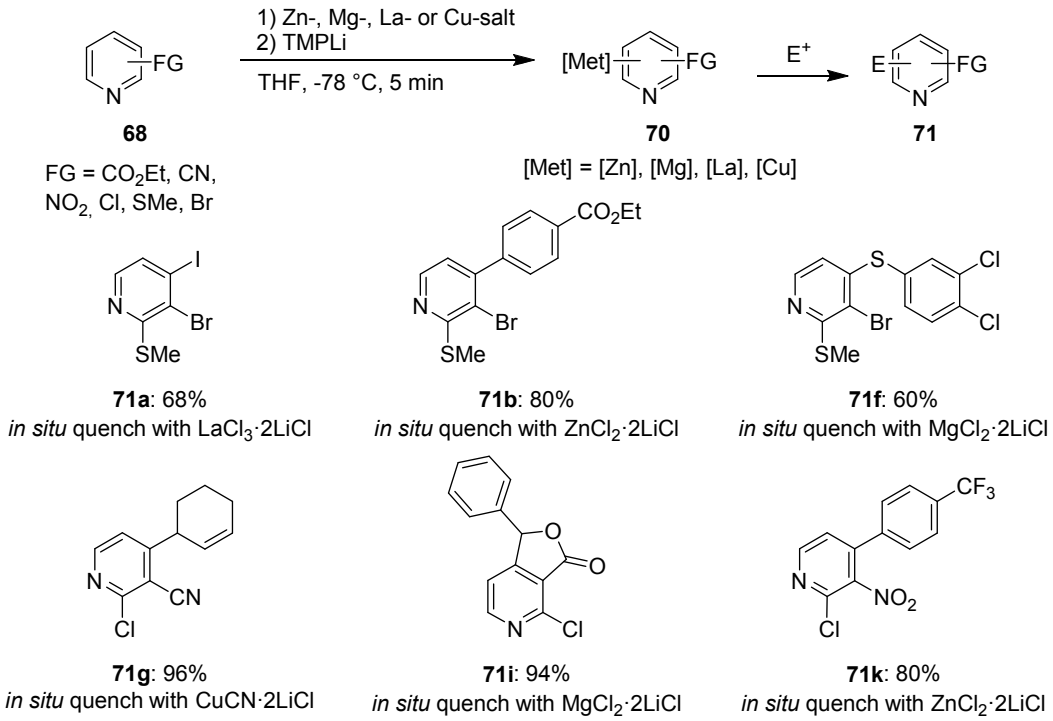


Scheme 107: Synthesis of the CB1 modifier analogue **67** starting from the previously prepared polyfunctional heterocycle **58b**; additional complexed salts are omitted for sake of clarity; PMBO-Na = sodium (*para*-methoxyphenyl)methanolate.

This methodology gives access to a variety of heteroarylmethylzinc derivatives not easily available otherwise. As these organozinc reagents, furthermore, give rise to a wide range of fused *N*- and *O*-heterocycles and well-tolerate functional groups, our strategy should find many applications in pharmaceutical, agrochemical and material science.

7.3 New in situ Metalations of Functionalized Arenes and Heterocycles with TMPLi in the Presence of $ZnCl_2$ and other Metal Salts

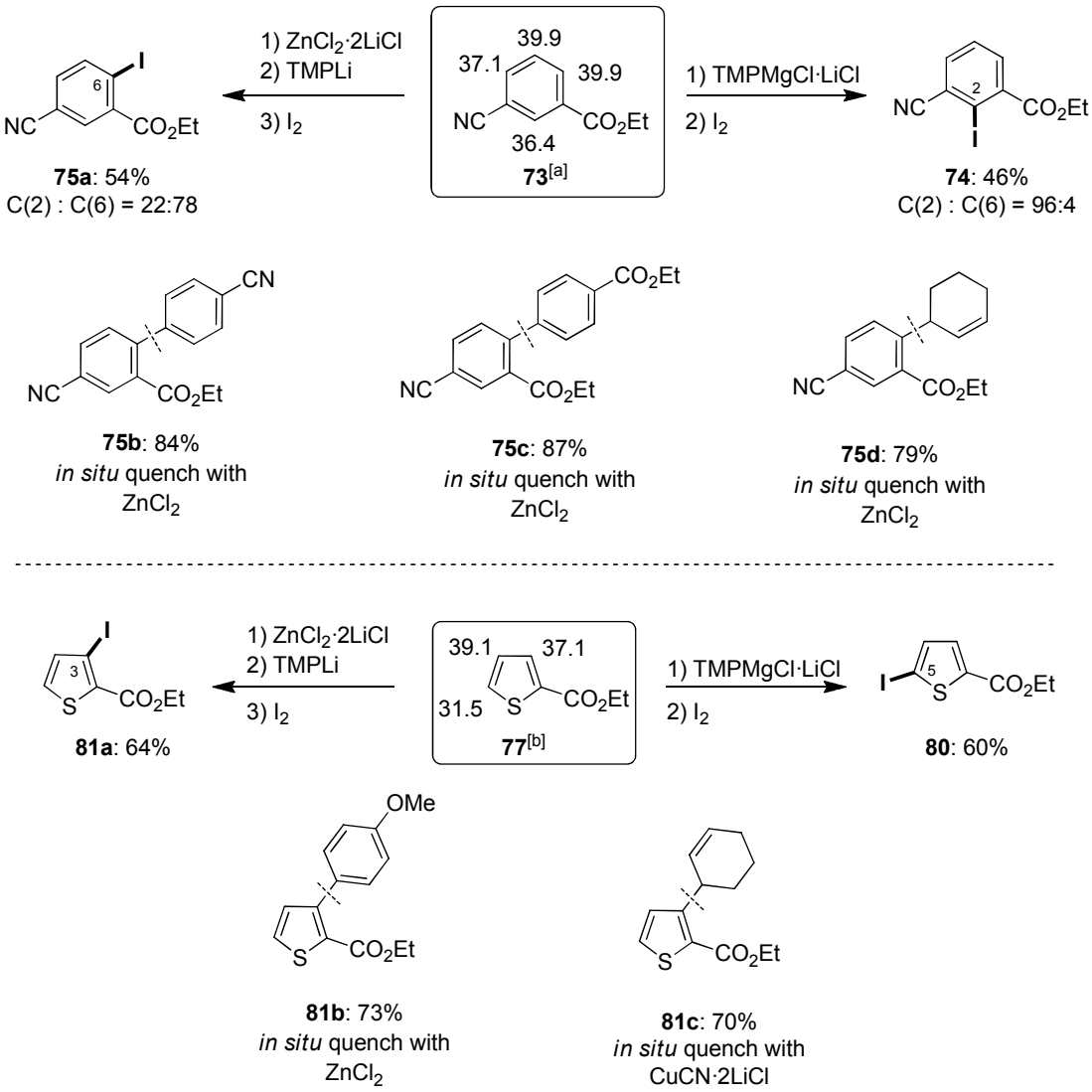
Often, the efficient metalation of *N*-heterocycles such as pyridines turns out to be problematic. Some of these heterocycles cannot successfully be metalated with moderately powerful bases such as TMP-derived magnesium and zinc amides, but in contrast, are prone to fast decomposition, even at -78 °C, upon treatment with stronger bases such as TMPLi and LDA. To this end, a practical and convenient procedure for the metalation of sensitive functionalized heterocycles **68** using TMPLi in the presence of metal salts such as $ZnCl_2$, $MgCl_2$, $LaCl_3$ and CuCN was developed, readily furnishing the corresponding Zn-, Mg-, La- and Cu-organometallics **70** (Scheme 108).



Scheme 108: Metalation of pyridines **68** using TMPLi in the presence of Zn-, Mg- and Cu-salts and subsequent functionalization with electrophiles.

When mixing the substrates **68** with a metal salt, the addition of TMPLi led first to a kinetic lithiation to generate rather unstable lithium derivatives, which were directly transmetalated with the metal salt present in the reaction mixture to afford the thermodynamically more stable organometallics **70**. These derivatives could then be subjected to various reactions including cross-couplings, allylations, acylations and addition reactions to aldhehydes affording the polyfunctional heterocycles **71** (Scheme **108**).

Furthermore, this lithiation/transmetalation strategy gave access to a variety of organometallics showing a regioselectivity different to the one obtained upon treatment with Zn- and Mg-amide bases. Due to thermodynamic effects, TMPMgCl·LiCl and the appropriate zinc bases allow the deprotonation of the most acidic protons. In contrast, metalation with TMPLi is of kinetic nature and often occurs on less sterically hindered positions, which might additionally be adjacent to a directing group such as esters and cyano-substituents. Thus, using this *in situ* trapping method, several (hetero)aromatic systems such as ethyl 3-cyanobenzoate (**73**) and ethyl thiophene-2-carboxylate (**77**) were readily functionalized in positions not accessible with moderately powerful Mg- and Zn-amides (Scheme 109).



Scheme 109: Regioselectivity switch in the metalation of ethyl 3-cyanobenzoate (**73**) and ethyl thiophene-2-carboxylate (**77**) by TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$ and $CuCN \cdot 2LiCl$, or by $TMPMgCl \cdot LiCl$. [a] Calculated pK_a values for H(2), H(4), H(5) and H(6); [b] Calculated pK_a values for H(2), H(3), and H(4).

We therefore think that this lithiation/transmetalation strategy is especially useful, since it allows the preparation of (hetero)aromatic organometallics not easily accessible otherwise, and thus, drastically expands the scope in the field of organic synthesis.

C. Experimental Section

1. GENERAL CONSIDERATIONS

All reactions were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun. Syringes which were used to transfer anhydrous solvents or reagents were purged three times with argon or nitrogen prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Unless otherwise indicated, all reagents were obtained from commercial sources. Liquid starting materials were distilled prior to use. Magnesium turnings (> 99.5%), magnesium powder (> 99%) and zinc dust (> 90%) were obtained from Riedel-de Haën. CuCN, $ZnCl_2$ and LiCl were obtained from Fluka.

1.1 SOLVENTS

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

$CHCl_3$ was predried over $CaCl_2$ and distilled from CaH_2.

1,4-Dioxane was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

MeOH was heated to reflux over magnesium methoxide and distilled.

NMP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled on a rotary evaporator prior to use.

1.2 REAGENTS

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid reagents were distilled prior to use.

***i*PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium.

***n*BuLi** solution in hexane was purchased from Rockwood Lithium.

LDA was prepared by the slow addition of *n*BuLi (2.3 M in hexane, 5.0 mmol) to a solution of di*iso*propylamine (0.7 mL, 5.0 mmol) in THF (5 mL) at -40 °C and stirring the reaction mixture for 30 min at -40 °C.

TMPMgCl·LiCl was prepared according to a literature procedure.[44a]

TMPLi was prepared by the slow addition of *n*BuLi (2.3 M in hexane, 5.0 mmol) to a solution of TMPH (0.85 mL, 5.0 mmol) in THF (5 mL) at -40 °C and stirring the reaction mixture for 30 min at -40 °C.

CuCN·2LiCl solution (1.0 M) was prepared by drying CuCN (7.17 g, 80.0 mmol) and LiCl (6.77 g, 160 mmol) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 80 mL anhydrous THF were added and stirring was continued until the salt was dissolved.

$ZnCl_2$ solution (1.0 M) was prepared by drying $ZnCl_2$ (136 g, 100 mmol) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL anhydrous THF were added and stirring was continued until the salt was dissolved.

$MgCl_2$ solution (0.5 M) was prepared by charging a *Schlenk*-flask with Mg-turnings (1.28 g, 52.5 mmol) and THF (50 mL). Freshly distilled dichloroethane (4.95 g, 50.0 mmol) was added slowly at room temperature (cooling with water bath, exothermic reaction). After the gas evolution had stopped, anhydrous THF (50 mL) was added and stirring was continued until the salt was dissolved.

LiCl solution (0.7 M) was prepared by drying by LiCl (8.6 g, 202 mmol) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, anhydrous THF (288 mL) was added and stirring was continued until the salt was dissolved.

1.3 CONTENT DETERMINATION OF ORGANOMETALLIC REAGENTS

Organozinc and organomagnesium reagents were titrated with I_2 in THF.[193]

Organolithium reagents were titrated with anhydrous 2-propanol and 1,10-phenanthroline as indicator in THF.[221]

LDA and **TMPLi** were titrated using phenyl benzamide as titrating agent and indicator in THF.

TMPMgCl·LiCl was titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[44a, 64]

1.4 CHROMATOGRAPHY

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from MERCK.

Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under 254 nm UV irradiation, by incubating the plates in an iodine chamber and/or by staining of the TLC plate with one of the reagents given below followed by heating with a heat gun:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

1.5 ANALYTICAL DATA

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to tetramethylsilane. The following

[221] H.-S. Lin, A. Paquette, *Synth. Commun*. **1994**, *24*, 2503.

abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), spt (septet), m (multiplet) as well as br (broadened).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV.

For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. Wavenumbers are reported in cm^{-1} starting at an absorption of 10%.

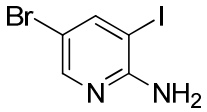
Melting points (mp) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.)

2. SYNTHESIS AND FULL-FUNCTIONALIZATION OF THE 7-AZAINDOLE SCAFFOLD *VIA* SELECTIVE METALATION AND SULFOXIDE/MAGNESIUM EXCHANGE

2.1 SYNTHESIS OF THE 7-AZAINDOLE RING

All reagents were obtained from commercial sources.

Preparation of 5-bromo-3-iodopyridin-2-amine (6)



Prepared according to a known literature procedure[157] from 2-amino-5-bromopyridine (**5**; 12.0 g, 67.0 mmol, 1.0 equiv), HIO_4 (3.86 g, 20.0 mmol, 0.3 equiv) and I_2 (8.50 g, 33.5 mmol, 0.5 equiv) in a mixture of acetonitrile and acetic acid to furnish **6** as beige solid (19.17 g, 96%).

mp: 112.0 °C-113.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.04 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 5.00 (s, 2H).

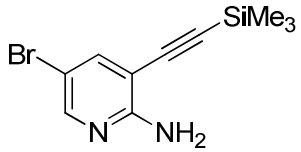
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 156.3, 148.4, 148.2, 107.3, 77.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3444, 3274, 3121, 2916, 2848, 2132, 1836, 1808, 1781, 1626, 1564, 1453, 1378, 1236, 1106, 1071, 1019, 883, 869, 741, 679.

MS (EI, 70 eV) m/z (%): 298 (3), 70 (10), 61 (19), 45 (12), 43 (100).

HRMS (EI): m/z calc. for [$C_5H_4BrIN_2$] 297.8603, found: 297.8595.

Preparation of 5-bromo-3-[2-(trimethylsilyl)ethynyl]pyridin-2-amine (8)



Prepared according to a known literature procedure[158] which was modified as follows: 5-bromo-3-iodopyridin-2-amine (**6**; 18.6 g, 62.3 mmol, 1.0 equiv), trimethylsilylacetylene (**7**; 6.73 g, 68.5 mmol, 1.1 equiv), CuI (238 mg, 1.25 mmol, 2 mol%) and $Pd(PPh_3)_2Cl_2$ (435 mg, 0.62 mmol, 1 mol%) were dissolved in triethylamine (100 mL) and stirred for 1 h at room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by recrystallization from *n*-heptane afforded **8** as brownish solid (15.91 g, 95%).

mp: 123.2 °C-130.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.02 (d, *J* = 2.4 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 5.07 (s, 2H), 0.25 (s, 9H).

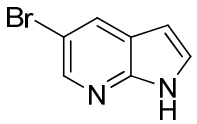
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 157.6, 148.3, 142.0, 106.8, 104.9, 102.9, 98.7, 0.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3454, 3289, 2956, 2148, 1625, 1548, 1457, 1397, 1246, 1193, 1117, 1099, 1060, 912, 900, 885, 760, 702, 658.

MS (EI, 70 eV) m/z (%): 271 (10), 270 (68), 269 (14), 268 (67) [M^+], 256 (13), 253 (17), 252 (100), 139 (12), 137 (12).

HRMS (EI): m/z calc. for [$C_{10}H_{13}BrN_2Si$] 268.0031, found: 268.0031.

Preparation of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (9)



To a solution of 5-bromo-3-[2-(trimethylsilyl)ethynyl]pyridin-2-amine (**8**; 5.38 g, 20.0 mmol, 1.0 equiv) in anhydrous NMP (10 mL) was slowly added NaH (1.12 g, 60 w% suspension in paraffin oil, 24.0 mmol, 1.2 equiv). The reaction mixture was heated to 80 °C for 1 h. After cooling to ambient temperature, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 5:1) afforded **9** as a colorless solid (3.16 g, 80%).

mp: 178.2-178.9°C

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.93 (s, 1H), 8.36 (d, *J* = 1.9 Hz, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 3.1 Hz, 1H), 6.49 (d, *J* = 3.1 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.8, 142.8, 131.3, 126.8, 122.2, 111.5, 100.5.

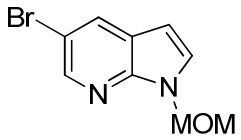
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3191, 3129, 3107, 3045, 2989, 2919, 2860, 1594, 1570, 1494, 1466, 1432, 1401, 1338, 1305, 1299, 1281, 1247, 1187, 1108, 1077, 1067, 917, 907, 901, 890, 879, 863, 779, 732, 670.

MS (EI, 70 eV) m/z (%): 196 (100) [M^+], 117 (42), 90 (13), 63 (11), 43 (29).

HRMS (EI): m/z calc. for [$C_7H_5BrN_2$] 195.9636, found: 195.9633.

2.2 FIRST ATTEMPTS TOWARDS THE FULL-FUNCTIONALIZATION OF THE 7-AZAINDOLE SCAFFOLD

Preparation of 5-bromo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (11)



The title compound was obtained applying two different methods.

Method A (starting from 8):

To a solution of 5-bromo-3-[2-(trimethylsilyl)ethynyl]pyridin-2-amine (**8**; 32.3 g, 120 mmol, 1.0 equiv) in anhydrous NMP (60 mL) was slowly added NaH (5.67 g, 60w% suspension in paraffin oil, 144 mmol, 1.2 equiv). The reaction mixture was heated to 80 °C for 1 h. After cooling to ambient temperature, NaH (4.80 g, 60w% suspension in paraffin oil, 120 mmol, 1.0 equiv) and methylchloromethylether (9.66 g, 120 mmol, 1.0 equiv) were added. After 1 h stirring at room temperature, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **11** as colorless oil (20.58 g, 71%).

Method B (starting from 9):

To a solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**9**; 3.94 g, 20.0 mmol) in anhydrous DMF (10 mL) were slowly added NaH (960 mg, 60w% suspension in paraffin oil, 24.0 mmol, 1.2 equiv) and methylchloromethylether (1.97 g, 24.0 mmol, 1.2 equiv). After 1 h stirring at ambient temperature, the reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **11** as colorless oil (4.37 g, 91%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.36 (d, *J* = 1.9 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 5.60 (s, 2H), 3.28 (s, 3H).

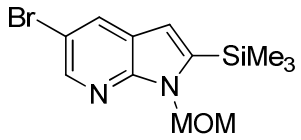
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.5, 143.7, 131.0, 129.3, 122.3, 112.3, 100.7, 75.0, 56.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2988, 2930, 2824, 1589, 1557, 1509, 1467, 1407, 1370, 1347, 1291, 1257, 1230, 1193, 1180, 1155, 1119, 1094, 1062, 996, 963, 912, 885, 784, 771, 754, 720, 668, 660.

MS (EI, 70 eV) m/z (%): 240 (49) [M^+], 212 (57), 211 (97), 210 (61), 209 (100), 131 (17), 45 (100), 43 (67).

HRMS (EI): m/z calc. for [$C_9H_9BrN_2O$] 239.9898, found: 239.9884.

Preparation of 5-bromo-1-(methoxymethyl)-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (10)



A solution of 5-bromo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**11**; 1.87 g, 7.7 mmol, 1.0 equiv) in anhydrous THF (15 mL) was added to freshly prepared TMPLi (8.5 mmol, 1.1 equiv) at -60 °C. The reaction mixture was allowed to warm up to -45 °C within 1 h. Then, chlorotrimethylsilane (**12a**; 1.0 g, 9.29 mmol, 1.2 equiv) was added at -45 °C and the mixture was allowed to warm to ambient temperature within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **10** as colorless oil (2.22 g, 88%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.32 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 6.64 (s, 1H), 5.69 (s, 2H), 3.25 (s, 3H) 0.38 (s, 9H).

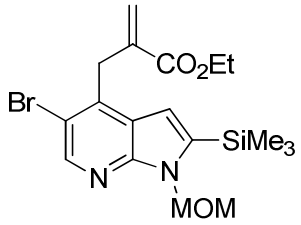
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.6, 144.0, 143.6, 130.5, 122.0, 111.9, 110.8, 74.1, 55.8, -0.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2952, 2898, 1557, 1480, 1441, 1409, 1393, 1357, 1330, 1297, 1261, 1248, 1215, 1198, 1180, 1159, 1118, 1090, 1043, 966, 921, 884, 837, 770, 765, 753, 695, 678.

MS (EI, 70 eV) m/z (%): 273 (15) [M^+], 246 (27), 245 (26), 244 (20), 243 (16), 61 (10), 45 (100), 43 (67).

HRMS (EI): m/z calc. for [$C_{12}H_{17}BrN_2OSi$] 312.0294, found: 312.0284.

Preparation of ethyl 2-((5-bromo-1-(methoxymethyl)-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)methyl)acrylate (13)



Freshly prepared TMPLi (2.2 mmol, 1.1 equiv) was added to a solution of 5-bromo-1-(methoxymethyl)-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**10**; 623 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (4 mL) -78 °C and the reaction mixture was allowed to stir at this temperature for 0.5 h. Then, $ZnCl_2$ (1.0 M in THF, 2.2 mmol, 1.1 equiv) was added at -78 °C and the mixture was allowed to warm to ambient temperature within 0.5 h, before it was cooled to -30 °C. Subsequently, CuCN·2LiCl (1.0 M in THF, 2.2 mmol, 1.1 equiv) and, after 15 min, ethyl (2-bromomethyl)acrylate (**12b**; 425 mg, 2.2 mmol, 1.1 equiv) were added. The reaction mixture was stirred at -30 °C for 1 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 14:1) afforded **13** as yellow oil (407 mg, 37%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.37 (s, 1H), 6.63 (s, 1H), 6.22 (s, 1H), 5.68 (s, 2H), 5.09 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 3.27 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.37 (s, 9H).

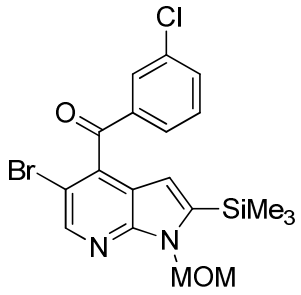
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.7, 149.9, 145.0, 143.3, 138.9, 136.5, 125.9, 122.2, 114.9, 110.0, 74.3, 61.1, 55.9, 34.2, 14.2, -0.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2954, 2931, 2900, 1739, 1714, 1700, 1696, 1684, 1653, 1635, 1628, 1624, 1576, 1569, 1565, 1558, 1476, 1472, 1465, 1457, 1448, 1437, 1416, 1394, 1363, 1352, 1301, 1276, 1249, 1224, 1194, 1173, 1130, 1092, 1048, 1026, 1011, 953, 916, 838, 770, 756, 720, 716, 695, 681, 671, 668, 660.

MS (EI, 70 eV) m/z (%): 424 (14) [M^+], 367 (18), 365 (27), 321 (18), 292 (16), 250 (42), 248 (43), 89 (26), 75 (32), 73 (100), 45 (87).

HRMS (EI): m/z calc. for [$C_{18}H_{25}N_2O_3Si$] 424.0818, found: 424.0815.

Preparation of (5-bromo-1-(methoxymethyl)-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)(3-chlorophenyl)methanone (14)



Freshly prepared TMPLi (2.2 mmol) was added to a solution of 5-bromo-1-(methoxymethyl)-2-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**10**; 623 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (4 mL) -78 °C and the reaction mixture was allowed to stir at this temperature for 0.5 h. Then, $ZnCl_2$ (1.0 M in THF, 2.2 mmol, 1.1 equiv) was added at -78 °C and the mixture was allowed to warm to ambient temperature within 0.5 h, before it was cooled to -30 °C. Subsequently, CuCN·2LiCl (1.0 M in THF, 2.2 mmol, 1.1 equiv) and, after 15 min, 3-chlorobenzoyl chloride (**12c**; 385 mg, 2.2 mmol, 1.1 equiv) were added. The reaction mixture was stirred at -30 °C for 1 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 14:1) afforded **14** as yellow solid (270 mg, 30%).

mp: 152.0 – 154.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.43 (s, 1H), 7.85 (s, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.60 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 6.42 (s, 1H), 5.72 (s, 2H), 3.30 (s, 3H) 0.34 (s, 9H).

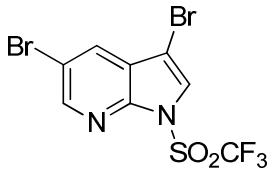
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 193.0, 150.3, 145.6, 144.9, 138.2, 137.0, 135.3, 134.2, 130.2, 129.7, 128.3, 119.4, 109.5, 108.1, 74.2, 56.1, -0.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1671, 1587, 1569, 1457, 1444, 1424, 1411, 1389, 1358, 1348, 1338, 1271, 1249, 1212, 1204, 1182, 1159, 1136, 1097, 1075, 1049, 1018, 998, 918, 908, 890, 879, 841, 821, 806, 783, 769, 764, 750, 742, 700, 675, 666, 656.

MS (EI, 70 eV) m/z (%): 450 (24) [M^+], 422 (43), 421 (32), 420 (31), 363 (27), 361 (22), 291 (18), 111 (19), 89 (37), 73 (87), 59 (39), 45 (100).

HRMS (EI): m/z calc. for [$C_{19}H_{20}BrClN_2O_2Si$] 450.0166, found: 450.0157.

Preparation of 3,5-dibromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15)



To a solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**9**; 828 mg, 3.0 mmol, 1.0 equiv) in $CHCl_3$ (35 mL) was added dropwise a solution of Br_2 (479 mg, 3.0 mmol, 1.0 equiv) in $CHCl_3$ (10 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was quenched with a sat. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The product was redissolved in CH_2Cl_2 (30 mL), and pyridine (0.39 mL, 4.8 mmol, 1.6 equiv) and trifluoromethanesulfonic anhydride (1.16 g, 3.3 mmol, 1.1 equiv) were added at 0 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by recrystallization from *n*-heptane afforded **15** as a brownish solid (1.15 g, 89%).

mp: 118.0 – 119.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.58 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 2.1 Hz, 1H), 7.59 (s, 1H).

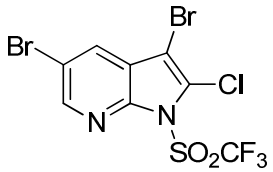
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.1, 145.4, 131.7, 126.4, 124.4, 119.2 (q, *J* (C – F) = 323.4 Hz), 117.7, 98.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3145, 2923, 1617, 1562, 1528, 1442, 1426, 1409, 1376, 1322, 1314, 1302, 1270, 1230, 1211, 1158, 1148, 1119, 1097, 1077, 1041, 951, 916, 890, 860, 812, 785, 775, 759, 751, 728, 688, 675.

MS (EI, 70 eV) m/z (%): 406 (37) [M^+], 344 (35), 342 (22), 277 (46), 275 (100), 273 (47), 196 (70), 194 (66), 115 (29), 88 (74), 63 (23).

HRMS (EI): m/z calc. for [$C_8H_3Br_2F_3N_2O_2S$] 405.8234, found: 405.8248.

Preparation of 3,5-dibromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (16)



To a solution of 3,5-dibromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**15**; 1.12 g, 2.74 mmol, 1.0 equiv) in THF (6 mL) was added TMPMgCl·LiCl (1.07 M in THF, 4.11 mmol, 1.5 equiv) at 0 °C and the reaction mixture was stirred at this temperature for 0.5 h. Then, neat benzenesulfonyl chloride (**12d**; 726 mg, 4.11 mmol, 1.5 equiv) was added and the reaction mixture allowed to warm to room temperature within 1 h, quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 50:1) afforded **16** as a colorless solid (1.04 g, 85%).

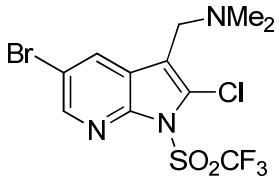
^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.55 (d, *J* = 2.2 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.7, 145.9, 130.6, 126.8, 123.0, 119.1 (q, *J* (C – F) = 323.7 Hz), 118.2, 100.2.

MS (EI, 70 eV) m/z (%): 440 (18) [M^+], 380 (31), 378 (49), 376 (20), 312 (20), 311 (73), 310 (31), 309 (96), 307 (40), 230 (33), 228 (29), 43 (100).

HRMS (EI): m/z calc. for [$C_8H_2Br_2ClF_3N_2O_2S$] 439.7844, found: 439.7836.

Preparation of 1-(5-bromo-2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylmethanamine (17)



A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with *N*,*N*,*N'*,*N'*-tetramethylmethanediamine (170 mg, 1.66 mmol, 1.1 equiv) and dissolved in anhydrous CH_2Cl_2 (2 mL). At 0 °C neat trifluoroacetic anhydride (349 mg, 1.66 mmol, 1.1 equiv) was added dropwise. After the highly exothermic reaction subsided and the smoke dissipated, the cooling was removed and the solution was allowed to warm up to 25 °C and stirred for 5 min. In a second flask, 3,5-dibromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**16**; 669 mg, 1.51 mmol,

1.0 equiv) was dissolved in anhydrous THF (3 mL) and *i*PrMgCl·LiCl (1.23 M in THF, 1.66 mmol, 1.1 equiv) was added at -78 °C. The reaction mixture was stirred at this temperature for 5 min. Then, the solution of previously prepared methylene(dimethyl)iminium trifluoroacetate was cannulated dropwise at -78 °C to the solution of the organometallic reagent. The reaction mixture was allowed to warm to room temperature within 1 h, quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 5:1, 2% triethylamine) afforded **17** as a yellowish solid (549 mg, 86%).

mp: 87.4 – 89.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.51 (d, *J* = 2.2 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 3.65 (s, 2H), 2.34 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.9, 146.7, 131.6, 126.1, 123.3, 119.3 (q, *J* (C – F) = 323.8 Hz), 117.7, 53.0, 45.2. (One signal not observed; possible coincidental isochronicity.)

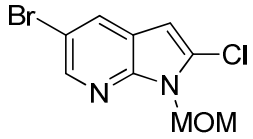
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2819, 2770, 1560, 1465, 1454, 1442, 1433, 1427, 1414, 1392, 1362, 1316, 1299, 1272, 1257, 1243, 1212, 1179, 1144, 1113, 1075, 1046, 1027, 1005, 972, 940, 900, 891, 852, 828, 782, 769, 763, 688, 680, 667.

MS (EI, 70 eV) m/z (%): 419 (63) [M^+], 379 (21), 377 (69), 375 (51), 315 (28), 313 (100), 311 (74), 288 (38), 286 (33), 246 (22), 245 (40), 244 (60), 243 (32), 242 (45), 208 (22), 102 (41), 58 (37).

HRMS (EI): m/z calc. for [$C_{11}H_{10}BrClF_3N_3O_2S$] 418.9318, found: 418.9312.

2.3 SYNTHESIS OF THE KEY 7-AZAINDOLE PRECURSOR

Preparation of 5-bromo-2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (19)



A solution of 5-bromo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**11**; 13.13 g, 54.5 mmol, 1.0 equiv) in anhydrous THF (109 mL) was added to the freshly prepared TMPLi (65.4 mmol, 1.2 equiv) at -60 °C. The reaction mixture was allowed to warm up to -45 °C within 1 h. Then, benzenesulfonyl chloride (**12 d**; 11.55 g, 65.4 mmol, 1.2 equiv) was added at -45 °C and the mixture was allowed to warm to ambient

temperature within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **19** as colorless solid (12.32 g, 82%).

mp: 68.4 - 69.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.32 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 6.42 (s, 1H), 5.66 (s, 2H), 3.33 (s, 3H).

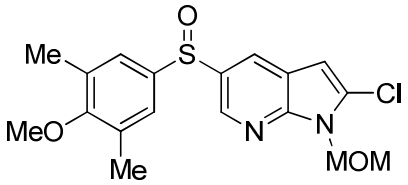
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.0, 143.8, 129.7, 128.6, 121.3, 113.2, 99.3, 72.2, 56.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3142, 3076, 2994, 2957, 2933, 2828, 1558, 1505, 1466, 1459, 1450, 1440, 1396, 1375, 1341, 1283, 1267, 1254, 1221, 1211, 1200, 1187, 1178, 1145, 1128, 1115, 1088, 1072, 1034, 918, 911, 886, 830, 785, 767, 750, 706, 670.

MS (EI, 70 eV) m/z (%): 273 (15) [M^+], 246 (27), 245 (26), 244 (20), 243 (16), 61 (10), 45 (100), 43 (67).

HRMS (EI): m/z calc. for [$C_9H_8BrClN_2O$] 273.9509, found: 273.9501.

Preparation of 2-chloro-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (21)



To a solution of 5-bromo-2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**19**; 12.32 g, 44.7 mmol, 1.0 equiv) in anhydrous THF (150 mL) was added *n*BuLi (2.48 M in THF, 44.7 mmol, 1.0 equiv) at -78 °C and the mixture was stirred for 5 min at this temperature. Then, $MgCl_2$ (0.5 M in THF, 49.2 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 0.5 h at -78 °C. The thus-prepared *Grignard* reagent was slowly added to a solution of 4-methoxy-3,5-dimethylbenzenesulfinyl chloride[172] (**20**; 10.75 g, 49.2 mmol, 1.1 equiv) in anhydrous THF (100 mL) at -78 °C and the reaction mixture was allowed to warm to -30 °C within 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 2:1) afforded **21** as yellowish solid (15.22 g, 90%).

mp: 98.4 -99.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.45 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 7.30 (s, 2H,), 6.53 (s, 1H), 5.70 (d, *J* = 11.2 Hz, 1H), 5.66 (d, *J* = 11.2 Hz, 1H), 3.69 (s, 3H), 3.34 (s, 3H), 2.28 (s, 6H).

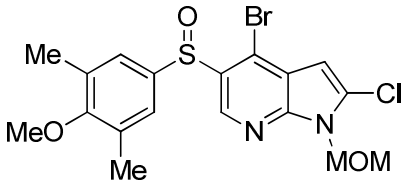
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.4, 148.6, 140.6, 139.4, 135.9, 132.7, 129.4, 125.0, 125.0, 120.1, 100.6, 72.4, 59.7, 56.9, 16.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2945, 2942, 2926, 2920, 2917, 2910, 1582, 1559, 1505, 1473, 1456, 1443, 1401, 1378, 1362, 1339, 1314, 1285, 1264, 1241, 1216, 1165, 1156, 1118, 1092, 1069, 1056, 1008, 962, 938, 917, 896, 873, 847, 835, 805, 787, 763, 755, 724, 718, 714, 711, 688, 668, 664, 660, 653.

MS (EI, 70 eV) m/z (%): 378 (75) [M^+], 330 (48), 300 (30), 299 (33), 285 (24), 185 (33), 168 (23), 151 (99), 45 (100).

HRMS (EI): m/z calc. for [$C_{18}H_{19}ClN_2O_3S$] 378.0805, found: 378.0807.

Preparation of 4-bromo-2-chloro-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (18)



To a solution of 2-chloro-5-(4-methoxy-3,5-dimethylbenzenesulfonyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**21**; 1.53 g, 4.0 mmol, 1.0 equiv) in anhydrous THF (15 mL) was added TMPMgCl·LiCl (1.21 M in THF, 6.0 mmol, 1.5 equiv) at -30 °C and the reaction mixture was stirred for 10 min at this temperature. Then, 1,2-dibromo-1,1,2,2-tetrachloroethane (**12e**; 1.95 g, 6.0 mmol, 1.5 equiv) was added and the mixture was allowed to warm to ambient temperature within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 2:1) afforded **18** as off-white solid (1.77 g, 97%).

mp: 156.7 - 158.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.67 (s, 1H), 7.41 (s, 2H), 6.56 (s, 1H), 5.72 (d, *J* = 11.0 Hz, 1H,), 5.65(d, *J* = 11.0 Hz, 1H), 3.69 (s, 3H), 3.35 (s, 3H), 2.27 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.7, 148.0, 141.4, 138.8, 134.2, 132.6, 129.6, 125.9, 122.5, 121.4, 100.5, 72.8, 59.7, 57.1, 16.3.

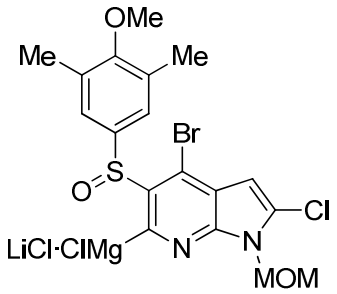
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3104, 2936, 2932, 1580, 1533, 1502, 1474, 1455, 1447, 1437, 1414, 1396, 1377, 1349, 1326, 1275, 1271, 1216, 1194, 1182, 1173, 1149, 1117, 1092, 1061, 1044, 1003, 942, 917, 879, 867, 821, 771, 762, 701, 676, 666.

MS (EI, 70 eV) m/z (%): 455 (26) [M$^+$], 442 (12), 410 (13), 408 (10), 380 (12), 379 (11), 183 (37), 167 (12), 152 (10), 151 (100), 45 (15).

HRMS (EI): m/z calc. for [$C_{18}H_{18}BrClN_2O_3S$] 455.9910, found: 455.9898.

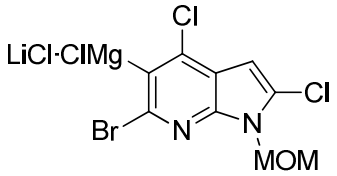
2.4 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Preparation of (4-bromo-2-chloro-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)magnesium(II) chloride (22)



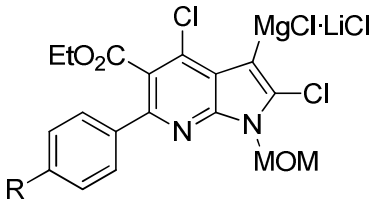
A dry and argon-flushed *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**18**; 1.0 equiv) in anhydrous THF (0.1 M). At -10 °C TMPMgCl·LiCl (1.21 M in THF, 1.5 or 1.7 equiv) was added and the reaction was stirred for 10 min at this temperature.

Typical procedure 2 (TP2): Preparation of (6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)magnesium(II) chloride (28b)



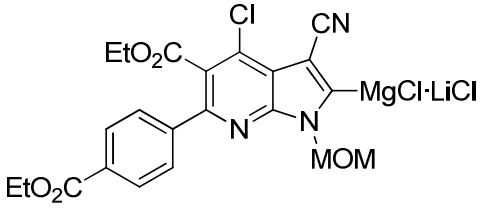
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**29**; 1.0 equiv) in anhydrous THF (0.1 M). At -40 °C *i*PrMgCl·LiCl (1.23 M in THF, 1.05 equiv) was added and the reaction mixture was stirred for 5 min at this temperature.

Typical procedure 3 (TP3): Preparation of (2,4-dichloro-5-(ethoxycarbonyl)-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)magnesium(II) chloride (34a) and (2,4-dichloro-6-(4-cyanophenyl)-5-(ethoxycarbonyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)magnesium(II) chloride (34b)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**32a**; 1.0 equiv) or ethyl 2,4-dichloro-6-(4-cyanophenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**32b**; 1.0 equiv) in anhydrous THF (0.1 M). At 0 °C *i*PrMgCl·LiCl (1.23 M in THF, 1.1 equiv) was added and the reaction mixture was stirred for 10 min at this temperature.

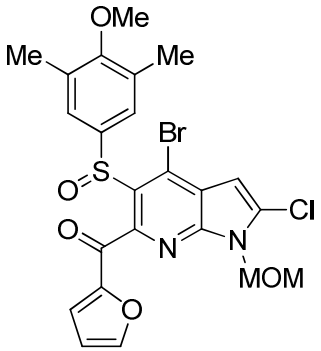
Typical procedure 4 (TP4): Preparation of (4-chloro-3-cyano-5-(ethoxycarbonyl)-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)magnesium(II) chloride (38)



A dry and argon flushed *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**37**; 1.0 equiv) in anhydrous THF (0.1 M). At -30 °C TMPMgCl·LiCl (1.21 M in THF, 1.1 equiv) was added and the reaction was stirred for 5 min at this temperature.

2.5 REGIOSELECTIVE FUNCTIONALIZATION OF POSITIONS 6,5 AND 4 OF THE 7-AZAINDOLE SCAFFOLD

Preparation of (4-bromo-2-chloro-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)(furan-2-yl)methanone (23a)



Prepared according to **TP1** from 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**18**; 229 mg, 0.50 mmol, 1.0 equiv) and TMPMgCl·LiCl (1.175 M in THF, 0.75 mmol, 1.5 equiv) within 10 min at -10 °C. Subsequently, $ZnCl_2$ (1 M in THF, 0.75 mmol, 1.5 equiv) was added and the mixture was stirred for 15 min at -10 °C. At -30 °C, CuCN·2LiCl (1.0 M in THF, 0.75 mmol, 1.5 equiv) and, after 15 min, furan-2-carbonyl chloride (**12f**; 98 mg, 0.75 mmol, 1.5 equiv) were added, and the mixture was allowed to warm to ambient temperature within 5 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 4:1) afforded **23a** as yellowish solid (175 mg, 63%).

mp: 118.0 – 126.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.69 (s, 1H), 7.56 (s, 2H), 7.27 (d, *J* = 2.9 Hz, 1H), 6.68 (s, 1H), 6.60 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.69 (s, 2H), 3.73 (s, 3H), 3.35 (s, 3H), 2.30 (s, 6H).

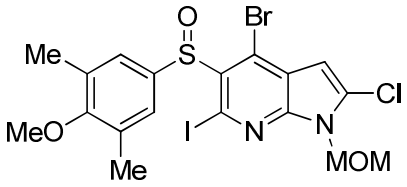
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 179.3, 159.0, 152.0, 149.4, 147.8, 145.6, 137.1, 133.2, 131.8, 126.9, 126.5, 125.0, 124.2, 121.7, 112.6, 101.4, 72.9, 59.7, 57.2, 16.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1666, 1568, 1529, 1494, 1467, 1457, 1423, 1377, 1360, 1276, 1265, 1241, 1218, 1188, 1165, 1146, 1119, 1094, 1081, 1056, 1030, 1013, 948, 915, 900, 888, 877, 868, 845, 796, 787, 771, 754, 740, 732, 686, 662.

MS (EI, 70 eV) m/z (%): 550 (4) [M^+], 439 (28), 438 (19), 437 (100), 436 (15), 435 (72), 403 (12), 401 (43), 399 (31), 183 (49), 168 (10), 95 (26), 91 (10), 45 (64).

HRMS (EI): m/z calc. for [$C_{23}H_{20}BrClN_2O_5S$] 549.9965, found: 549.9965

Preparation of 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxy-methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (23b)



Prepared according to **TP1** from 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**18**; 1.37 g, 3.0 mmol, 1.0 equiv) and TMPMgCl·LiCl (1.21 M in THF, 5.10 mmol, 1.7 equiv) within 10 min at -10 °C. Subsequently, neat I_2 (1.52 g, 6.0 mmol, 2.0 equiv) was added at this temperature and the mixture was allowed to warm up to ambient temperature within 1 h. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 4:1) afforded **23b** as colorless solid (1.06 g, 61%).

mp: 173.4 - 177.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30 (s, 2H), 6.58 (s, 1H), 5.65 (d, *J* = 11.0 Hz, 1H), 5.62 (, *J* = 11.0 Hz, 1H), 3.71 (s, 3H), 3.36 (s, 3H), 2.27 (s, 6H).

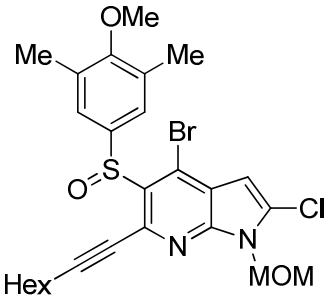
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.9, 147.3, 136.9, 133.4, 132.1, 130.1, 125.8, 125.5, 123.6, 101.4, 72.9, 59.7, 57.3, 29.7, 16.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2918, 1571, 1521, 1494, 1476, 1464, 1450, 1430, 1396, 1368, 1266, 1211, 1202, 1176, 1150, 1119, 1092, 1081, 1060, 1046, 1000, 952, 918, 886, 875, 868, 783, 771, 760, 746, 717, 687.

MS (EI, 70 eV) m/z (%): 582 (34) [M^+], 440 (48), 438 (29), 409 (20), 407 (25), 183 (88), 151 (100), 128 (58), 127 (41), 45 (25).

HRMS (EI): m/z calc. for [$C_{18}H_{17}BrClIN_2O_3S$] 581.8876, found: 581.8874.

Preparation of 4-bromo-2-chloro-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-6-(oct-1-yn-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (25)



To a solution of 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**23b**; 1.17 g, 2.0 mmol, 1.0 equiv) in anhydrous THF (20 mL) were added triethylamine (2.80 mL, 20.0 mmol, 10 equiv), oct-1-yne (**24**; 264 mg, 2.4 mmol, 1.0 equiv), CuI (229 mg, 0.12 mmol, 6 mol%) and $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 3 mol%) and the mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 4:1) afforded **25** as a yellowish solid (1.04 g, 92%).

mp: 91.7 - 99.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.28 (s, 2H), 6.57 (s, 1H), 5.65 (s, 2H), 3.70 (s, 3H), 3.34 (s, 3H), 2.48 (t, J = 7.1 Hz, 2H), 2.27 (s, 6H), 1.67-1.58 (m, 2H), 1.48-1.38 (m, 2H), 1.29-1.23 (m, 4H), 0.87-0.82 (m, 3H).

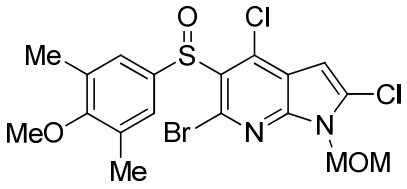
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.6, 146.7, 137.4, 137.4, 134.2, 131.7, 130.6, 125.4, 125.1, 122.7, 101.4, 99.3, 77.9, 72.5, 59.7, 57.0, 31.3, 28.8, 28.0, 22.5, 19.9, 16.3, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2936, 2855, 2824, 2230, 1576, 1521, 1490, 1477, 1465, 1454, 1434, 1408, 1386, 1352, 1310, 1266, 1219, 1170, 1127, 1095, 1071, 1035, 1010, 944, 914, 895, 874, 863, 786, 757, 729, 707, 688, 676, 652.

MS (EI, 70 eV) m/z (%): 564 (7) [M^+], 453 (26), 451 (24), 437 (22), 46 (100), 45 (22), 44 (30), 43 (24).

HRMS (EI): m/z calc. for [$C_{26}H_{30}BrClN_2O_3S$] 564.0849, found: 564.0839.

Preparation of 6-bromo-2,4-dichloro-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (27a)



Freshly prepared TMPLi (16.74 mmol, 1.3 equiv) was added to a solution of 4-bromo-2-chloro-5-(4-methoxy-3,5-dimethylbenzenesulfonyl)-1-(methoxy-methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**18**; 5.90 g, 12.9 mmol, 1.0 equiv) and 1,1,2-trichloro-1,2,2-trifluoroethane (**12g**; 3.62 g, 19.3 mmol, 1.5 equiv) in anhydrous THF (130 mL) at -78 °C. The mixture was allowed to warm to ambient temperature within 2 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded compound **27a** as colorless solid (5.78 g, 91%).

mp: 165.3 - 166.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32 (s, 2H), 6.62 (s, 1H), 5.65 (d, *J* = 11.2 Hz, 1H), 5.62 (d, *J* = 11.2 Hz, 1H), 3.72 (s, 3H), 3.37 (s, 3H), 2.29 (s, 6H).

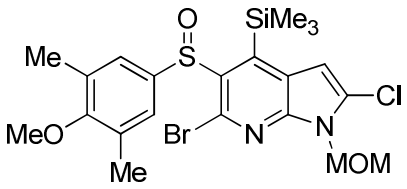
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.9, 147.0, 138.1, 136.7, 35.7, 132.1, 130.9, 129.9, 125.1, 120.6, 99.8, 72.8, 59.7, 57.2, 16.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2946, 2931, 1571, 1528, 1497, 1481, 1466, 1449, 1433, 1399, 1380, 1361, 1348, 1275, 1236, 1210, 1183, 1169, 1157, 1126, 1092, 1085, 1062, 1048, 1008, 1000, 981, 971, 945, 917, 885, 876, 868, 834, 813, 808, 785, 775, 756, 750, 692, 668, 661.

MS (EI, 70 eV) m/z (%): 490 (7) [M^+], 183 (78), 151 (100), 45 (35).

HRMS (EI): m/z calc. for [$C_{18}H_{17}BrCl_2N_2O_3S$] 489.9520, found: 489.9511.

Preparation of 6-bromo-2-chloro-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-1-(methoxymethyl)-4-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (27b)



Freshly prepared TMPLi (0.65 mmol, 1.3 equiv) was added to a solution of 4-bromo-2-chloro-6-iodo-5-(4-methoxy-3,5-dimethylbenzenesulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**18**; 229 mg, 0.50 mmol, 1.0 equiv) and chlorotrimethylsilane

(**12a**; 218 mg, 2.0 mmol, 4.0 equiv) in anhydrous THF (5 mL) at -78 °C, and the reaction mixture was allowed to warm to ambient temperature within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **27b** as yellowish solid (209 mg, 79%).

mp: 149.0-151.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.99 (s, 2H), 6.82 (s, 1H), 5.66 (s, 2H), 3.72 (s, 3H), 3.35 (s, 3H), 2.25 (s, 6H), 0.60 (s, 9H).

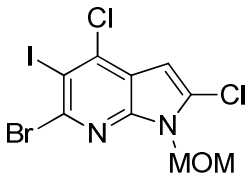
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.4, 150.1, 146.1, 136.9, 136.6, 135.7, 131.8, 128.8, 125.8, 122.9, 102.8, 72.5, 59.8, 57.2, 16.3, 3.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2990, 2937, 1541, 1501, 1452, 1420, 1408, 1369, 1350, 1252, 1217, 1124, 1093, 1066, 1045, 1013, 961, 880, 864, 848, 836, 778, 755, 689.

MS (EI, 70 eV) m/z (%): 529 (7) [M+H$^+$], 453 (26), 451 (24), 437 (22), 46 (100), 45 (22), 44 (30), 43 (24).

HRMS (EI): m/z calc. for [$C_{21}H_{27}BrClN_2O_3SSi$] 529.0384 [M+H]$^+$, found: 529.0379.

Preparation of 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (29)



To a solution of 6-bromo-2,4-dichloro-5-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**27a**; 246 mg, 0.50 mmol, 1.0 equiv) in anhydrous THF (5 mL) was added *i*PrMgCl·LiCl (1.21 M in THF, 0.50 mmol, 1.0 equiv) at -90 °C. The reaction mixture was stirred for 2 min at this temperature. Then, $ZnCl_2$ (1.0 M in THF, 0.50 mmol, 1.0 equiv) was added and the solution was stirred for 15 min at -90 °C, before it was allowed to warm to ambient temperature within 1 h. Neat I_2 (254 mg, 1.0 mmol, 2.0 equiv) was added and after 0.5 h, the crude reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 60:1) afforded **29** as colorless solid (131 mg, 60%).

mp: 142.1- 143.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.54 (s, 1H), 5.62 (s, 2H), 3.34 (s, 3H).

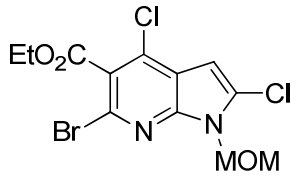
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.1, 141.5, 140.5, 129.0, 118.9, 99.5, 95.0, 72.7, 57.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3132, 3003, 2939, 2894, 2814, 1581, 1531, 1500, 1472, 1461, 1446, 1426, 1400, 1376, 1293, 1260, 1232, 1199, 1187, 1173, 1156, 1115, 1107, 1077, 1054, 957, 950, 901, 877, 838, 809, 789, 779, 773, 756, 735, 676.

MS (EI, 70 eV) m/z (%): 434 (2) [M^+], 61 (14), 45 (32), 43 (100).

HRMS (EI): m/z calc. for [$C_9H_6BrCl_2IN_2O$] 433.8085, found: 433.8084.

Preparation of ethyl-6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (30a)



Prepared according to **TP2** from 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**29**; 2.10 g, 4.82 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.23 M in THF, 5.06 mmol, 1.05 equiv) within 5 min at -40 °C. Subsequently, ethyl cyanoformate (**12h**; 955 mg, 9.64 mmol, 2.0 equiv) was added and the mixture was stirred for 30 min at -40 °C. The crude reaction mixture was allowed to warm to ambient temperature within 1 h, quenched with H_2O and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 40:1) afforded **30a** as colorless oil (1.75 g, 95%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.56 (s, 1H), 5.61 (s, 2H), 4.45 (q, J = 7.2 Hz, 2H), 3.30 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

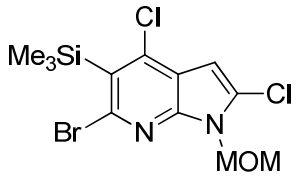
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 164.9, 146.1, 132.9, 131.1, 129.2, 125.9, 117.9, 99.2, 72.7, 62.5, 57.0, 13.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3127, 2981, 2936, 2827, 1732, 1592, 1538, 1496, 1462, 1410, 1394, 1366, 1357, 1313, 1295, 1278, 1241, 1205, 1180, 1160, 1127, 1089, 1048, 1021, 993, 985, 910, 860, 834, 781, 766, 750, 690, 668, 657.

MS (EI, 70 eV) m/z (%): 380 (7) [M^+], 352 (19), 350 (12), 61 (11), 45 (100).

HRMS (EI): m/z calc. for [$C_{12}H_{11}BrCl_2N_2O_3$] 379.9330, found: 379.9330.

Preparation of 6-bromo-2,4-dichloro-1-(methoxymethyl)-5-(trimethylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine (30b)



Prepared according to **TP2** from 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**29**; 436 mg, 1.00 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.21 M in THF, 1.05 mmol, 1.05 equiv) within 5 min at -40 °C. Subsequently, chlorotrimethylsilane (**12a**; 1.09 g, 10.0 mmol, 10 equiv) was added and the mixture was stirred for 30 min at -40 °C. The crude reaction mixture was allowed to warm to ambient temperature within 1 h, quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 60:1) afforded **30b** as colorless oil (371 g, 97%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.53 (s, 1H), 5.60 (s, 2H), 3.34 (s, 3H), 0.57 (s, 9H).

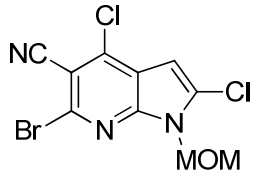
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.6, 142.8, 141.5, 127.6, 127.1, 119.3, 99.4, 72.4, 57.0, 3.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2991, 2942, 2899, 2827, 1583, 1532, 1498, 1458, 1428, 1397, 1374, 1344, 1301, 1250, 1236, 1195, 1175, 1152, 1126, 1119, 1088, 1046, 968, 917, 883, 841, 767, 746, 686, 652.

MS (EI, 70 eV) m/z (%): 380 (9) [M^+], 367 (18), 365 (11), 337 (14), 335 (14), 45 (100).

HRMS (EI): m/z calc. for [$C_{12}H_{15}BrCl_2N_2OSi$] 379.9514, found: 379.9508.

Preparation of 6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (30c)



Prepared according to **TP2** from 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**29**; 217 mg, 0.50 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.24 M in THF, 0.50 mmol, 1.0 equiv) within 5 min at -40 °C. Subsequently, *p*-toluenesulfonyl cyanide (**12i**; 182 mg, 1.00 mmol, 2.0 equiv) was added and the mixture was stirred for 30 min at -40 °C. The crude reaction mixture was allowed to warm to ambient

temperature within 1 h, quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **30c** as colorless solid (114 mg, 68%).

mp : 150.3-141.1°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.67 (s, 1H), 5.66 (s, 2H), 3.36 (s, 3H).

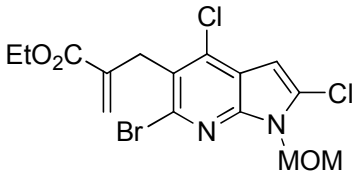
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.9, 139.7, 136.8, 130.8, 118.1, 114.6, 107.2, 99.8, 73.1, 57.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3112, 2961, 2933 , 2232 , 1986, 1588, 1534, 1495, 1465, 1451, 1436, 1412, 1397,1360, 1323, 1277, 1232, 1191, 1174, 1134, 1090, 1043, 1029, 1018, 967, 919, 904, 807, 791, 766, 759, 748, 710, 675, 663, 656.

MS (EI, 70 eV) m/z (%): 333 (5) [M^+], 305 (11), 61 (11), 45 (100), 43 (65).

HRMS (EI): m/z calc. for [$C_{10}H_6BrCl_2N_3O$] 332.9071, found: 332.9067.

Preparation of ethyl-2-((6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)acrylate (30d)



Prepared according to **TP2** from 6-bromo-2,4-dichloro-5-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**29**; 217 mg, 0.50 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.24 M in THF, 0.50 mmol, 1.0 equiv) within 5 min at -40 °C. Subsequently, $ZnCl_2$ (1.0 M in THF, 0.60 mmol, 1.2 equiv) was added and the reaction was allowed to warm up to -30°C within 15 min. Then, CuCN·2LiCl (1.0 M in THF, 0.60 mmol, 1.2 equiv) was added and the solution was stirred for 15 min at -30°C, before ethyl-2-(bromomethyl)acrylate (**12b**; 0.193 g, 1.00 mmol, 2.0 equiv) was added. The crude reaction mixture was allowed to warm to ambient temperature within 3 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 40:1) afforded **30d** as colorless oil (167 mg, 78%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.54 (s, 1H), 6.21 – 6.20 (m, 1H), 5.63 (s, 2H), 4.97 – 4.96 (m, 1H), 4.28 (q, *J* =7.2 Hz, 2H), 4.03 – 4.02 (m, 2H), 3.37 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

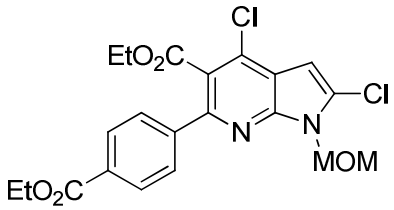
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.6, 145.5, 138.3, 136.6, 136.2, 128.3, 125.8, 124.6, 119.0, 98.9, 72.6, 61.0, 57.0, 34.4, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3127, 2988, 2943, 2907, 1712, 1635, 1592, 1539, 1497, 1399, 1297, 1267, 1181, 1128, 1098, 1031, 948, 912, 867, 767, 704.

MS (EI, 70 eV) m/z (%): 420 (10) [M^+], 343 (47), 342 (15), 341 (72), 315 (35), 313 (58), 283 (20), 45 (100).

HRMS (EI): m/z calc. for [$C_{15}H_{15}BrCl_2N_2O_3$] 419.9643, found: 419.9653.

Preparation of ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (32a)



To a solution of ethyl-4-iodobenzoate (1.17 g, 4.23 mmol, 1.3 equiv) in THF (8 mL) was added *i*PrMgCl·LiCl (1.28 M in THF, 4.55 mmol, 1.4 equiv) at -20°C. The mixture was stirred for 0.5 h at this temperature. Then, $ZnCl_2$ (1.0 M in THF, 4.55 mmol, 1.4 equiv) was added and the reaction was allowed to warm up to ambient temperature. The thus-prepared zinc reagent **31a** was then added to a solution of ethyl-6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**30a**; 1.24 g, 3.25 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (112 mg, 3 mol%) in anhydrous THF (4 mL). The reaction mixture was stirred for 5 h at room temperature, quenched with H_2O and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **32a** as brown solid (1.44 g, 98%).

mp: 65.1 - 85.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.10 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 6.67 (s, 1H), 5.73 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

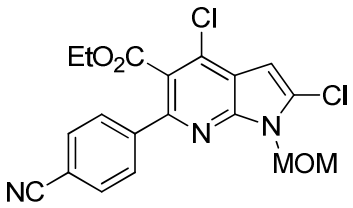
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.7, 166.3, 150.5, 147.1, 143.7, 133.2, 130.6, 129.7, 129.5, 128.6, 123.3, 118.0, 99.3, 72.6, 62.1, 61.1, 57.1, 14.3, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3403, 3140, 2981, 2930, 2909, 2872, 2828, 1713, 1608, 1592, 1571, 1539, 1489, 1463, 1413, 1393, 1364, 1337, 1308, 1292, 1260, 1190, 1177, 1140, 1124, 1104, 1081, 1039, 1023, 988, 925, 911, 875, 837, 789, 753, 718, 692, 671.

MS (EI, 70 eV) m/z (%): 450 (7) [M^+], 422 (5), 421 (7), 420 (7), 420 (7), 419 (6), 45 (100).

HRMS (EI): m/z calc. for [$C_{21}H_{20}Cl_2N_2O_5$] 450.0749, found: 450.0742.

Preparation of ethyl-2,4-dichloro-6-(4-cyanophenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (32b)



To a solution of 4-bromobenzonitrile (237 mg, 1.3 mmol, 1.3 equiv) in THF (3 mL) was added *i*PrMgCl·LiCl (1.28 M in THF, 1.37 mmol, 1.37 equiv) at 0°C. The mixture was stirred for 3 h at this temperature. Then, $ZnCl_2$ (1.0 M in THF, 1.30 mmol, 1.3 equiv) was added and the reaction was allowed to warm up to ambient temperature. The so-prepared zinc reagent **31b** was then added to a solution of ethyl-6-bromo-2,4-dichloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**30a**; 382 mg, 1.0 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (35 mg, 3 mol%) in anhydrous THF (1 mL). The reaction mixture was stirred for 16 h at room temperature, quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **32b** as colorless solid (263 mg, 65%).

mp: 125.9 -127.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.76 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 6.69 (s, 1H), 5.72 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.5, 149.4, 147.1, 143.9, 133.4, 132.1, 130.2, 129.3, 123.3, 118.6, 118.4, 112.4, 99.4, 72.6, 62.3, 57.1, 13.8.

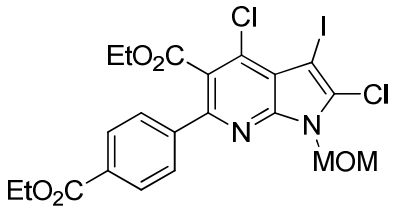
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3121, 2983, 2955, 2934, 2926, 2226, 1731, 1605, 1596, 1535, 1495, 1463, 1440, 1417, 1403, 1390, 1377, 1358, 1340, 1315, 1306, 1274, 1256, 1192, 1178, 1146, 1116, 1088, 1049, 1020, 1014, 993, 970, 926, 914, 855, 842, 813, 799, 789, 771, 761, 742, 736, 701, 682, 668, 659.

MS (EI, 70 eV) m/z (%): 403 (19) [M^+], 375 (15), 374 (14), 373 (21), 372 (16), 45(100), 43 (22).

HRMS (EI): m/z calc. for [$C_{19}H_{15}Cl_2N_3O_3$] 403.0490, found: 403.0483.

2.6 REGIOSELECTIVE FUNCTIONALIZATION OF POSITIONS 3 AND 2 OF THE 7-AZAINDOLE SCAFFOLD

Preparation of ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (33a)



To a solution of ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**32a**; 903 mg, 2.00 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added recrystallized *N*-iodosuccinimide (990 mg, 4.40 mmol, 2.2 equiv). The reaction mixture was stirred 15 h at ambient temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **33a** as colorless solid (1.00 g, 87%).

mp: 146.3 -148.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.10 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 5.77 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

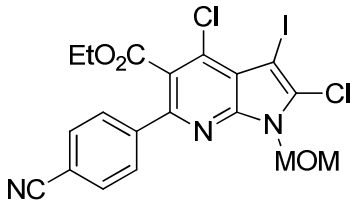
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.4, 166.2, 150.5, 146.8, 143.2, 134.3, 134.2, 130.8, 129.6, 128.6, 124.5, 116.3, 73.7, 62.2, 61.2, 57.3, 55.0, 14.3, 13.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2974, 2932, 2853, 1712, 1609, 1582, 1572, 1527, 1507, 1495, 1476, 1464, 1454, 1414, 1408, 1392, 1371, 1366, 1355, 1335, 1304, 1296, 1273, 1258, 1228, 1172, 1155, 1123, 1099, 1049, 1027, 1009, 975, 939, 910, 902, 885, 874, 862, 822, 800, 790, 779, 761, 720, 696, 674, 666, 657.

MS (EI, 70 eV) m/z (%): 576 (44) [M^+], 546 (30), 421 (30), 420 (21), 419 (26), 45 (100), 44(23), 43 (52).

HRMS (EI): m/z calc. for [$C_{21}H_{19}Cl_2IN_2O_5$] 575.9716, found: 575.9717.

Preparation of ethyl 2,4-dichloro-6-(4-cyanophenyl)-3-iodo-1-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (33b)



To a solution of ethyl-2,4-dichloro-6-(4-cyanophenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**32b**; 950 mg, 2.35 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added recrystallized *N*-iodosuccinimide (1.16 g, 5.17 mmol, 2.2 equiv). The reaction mixture was stirred for 15 h at ambient temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **33b** as orange solid (1.10 g, 83 %).

mp: 198.3 -199.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.78 – 7.71 (m, 4H), 5.76 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

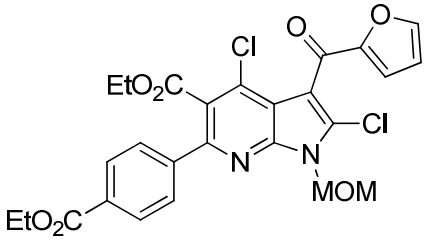
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.37, 149.5, 147.1, 143.9, 134.8, 132.2, 129.5, 124.7, 118.7, 116.9, 112.7, 108.5, 74.1, 62.6, 57.5, 55.4, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3041, 2991, 2969, 2940, 2854, 2226, 1950, 1726, 1605, 1582, 1532, 1506, 1481, 1461, 1439, 1415, 1386, 1371, 1337, 1325, 1304, 1275, 1261, 1184, 1164, 1103, 1057, 1025, 1013, 1002, 970, 912, 853, 833, 814, 800, 783, 768, 699, 686, 659.

MS (EI, 70 eV) m/z (%): 529(29) [M^+], 499 (14), 45 (100).

HRMS (EI): m/z calc. for [$C_{19}H_{14}Cl_2IN_3O_3$] 528.9457, found: 528.9458.

Preparation of ethyl-2,4-dichloro-6-[4-(ethoxycarbonyl)phenyl]-3-(furan-2-carbonyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (35a)



Prepared according to **TP3** from ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**33a**; 1.02 g,

1.73 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.23 M in THF, 1.90 mmol, 1.1 equiv) within 10 min at 0 °C. Subsequently, $ZnCl_2$ (1 M in THF, 2.08 mmol, 1.2 equiv) was added, the reaction was stirred for 15 min at 0 °C and then cooled to -30°C. CuCN·2LiCl (1 M in THF, 2.08 mmol, 1.2 equiv) was added and the reaction was stirred for 15 min at -30°C, before furan-2-carbonyl chloride (**12f**; 451 mg, 3.46 mmol, 2.0 equiv) was added subsequently. The mixture was allowed to warm to ambient temperature within 16 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 4:1) afforded **35a** as yellow solid (647 mg, 68%).

mp: 99.1 - 100.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, *J* = 7.7 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.65 (s, 1H), 7.21 (d, *J* = 3.5 Hz, 1H), 6.60 (m, 1H), 5.80 (s, 2H), 4.40 (q, *J* = 7.0 Hz, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.43 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

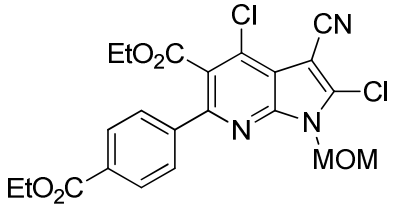
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 176.6, 166.3, 166.1, 153.3, 151.4, 147.5, 146.4, 143.1, 134.1, 130.9, 130.9, 129.6, 128.6, 125.2, 120.2, 115.9, 112.9, 112.2, 73.0, 62.2, 61.2, 57.5, 14.3, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1726, 1712, 1644, 1610, 1597, 1563, 1536, 1514, 1465, 1456, 1421, 1409, 1392, 1366, 1349, 1311, 1275, 1248, 1200, 1179, 1164, 1133, 1107, 1083, 1061, 1048, 1031, 1015, 980, 941, 916, 882, 869, 845, 818, 802, 782, 765, 739, 721, 708, 692, 678, 653.

MS (EI, 70 eV) m/z (%): 544 (38) [M^+], 515 (26), 514 (27), 513 (31), 479 (42), 45 (100), 43 (44).

HRMS (EI): m/z calc. for [$C_{26}H_{22}Cl_2N_2O_7$] 544.0804, found: 544.0802.

Preparation of ethyl-2,4-dichloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (35b)



Prepared according to **TP3** from ethyl-2,4-dichloro-6-(4-(ethoxycarbonyl)phenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**33a**; 5.19 g, 9.00 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.23 M in THF, 9.90 mmol, 1.1 equiv) within

10 min at 0 °C. Subsequently, *p*-toluenesulfonyl cyanide (**12i**; 2.44 g, 13.5 mmol, 1.5 equiv) was added and the resulting mixture was stirred for 30 min at 0 °C, before it was allowed to warm to ambient temperature within 3 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **35b** as yellowish solid (3.58 g, 84%).

mp: 130.4 - 135.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.40 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

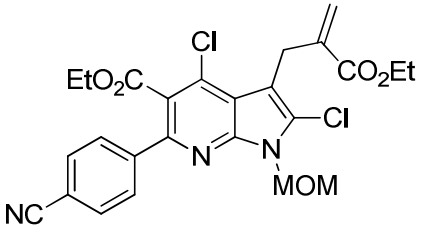
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.0, 165.7, 152.8, 145.9, 142.6, 138.1, 134.5, 131.2, 129.6, 128.6, 125.7, 115.8, 112.1, 86.5, 73.5, 62.5, 61.3, 57.7, 14.3, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2987, 2942, 2231, 1714, 1611, 1594, 1541, 1507, 1467, 1460, 1449, 1420, 1395, 1360, 1340, 1312, 1276, 1263, 1246, 1199, 1186, 1179, 1155, 1136, 1124, 1114, 1104, 1057, 1042, 1022, 1011, 987, 967, 951, 918, 907, 878, 869, 859, 846, 831, 820, 800, 792, 775, 764, 720, 697, 683, 652.

MS (EI, 70 eV) m/z (%): 475 (15) [M^+], 445 (11), 410 (12), 45 (100).

HRMS (EI): m/z calc. for [$C_{22}H_{19}Cl_2N_3O_5$] 475.0702, found: 475.0693.

Preparation of ethyl 2,4-dichloro-6-(4-cyanophenyl)-3-(2-(ethoxycarbonyl)allyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (36)



Prepared according to **TP3** from ethyl 2,4-dichloro-6-(4-cyanophenyl)-3-iodo-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**33b**; 530 mg, 1.00 mmol, 1.0 equiv) and *i*PrMgCl·LiCl (1.23 M in THF, 1.1 mmol, 1.1 equiv) within 10 min at 0 °C. Subsequently, $ZnCl_2$ (1.0 M in THF, 1.2 mmol, 1.2 equiv) was added and the reaction was stirred at 0°C for 15 min, before it was cooled to -30 °C. Then, CuCN·2LiCl (1.0 M in THF, 1.2 mmol, 1.2 equiv) was added and the solution was stirred for 15 min at -30 °C, before ethyl-2-(bromomethyl)acrylate (**12b**; 232 mg, 1.2 mmol, 1.2 equiv) was added. The crude reaction mixture was allowed to warm to ambient temperature within

1 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **36** as yellow solid (356 mg, 69%).

mp: 113.6 -115.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.78 – 7.70 (m, 4H), 6.24 (s, 1H), 5.73 (s, 2H), 5.10 (s, 1H), 4.31 – 4.18 (m, 4H), 3.98 (s, 2H), 3.36 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H).

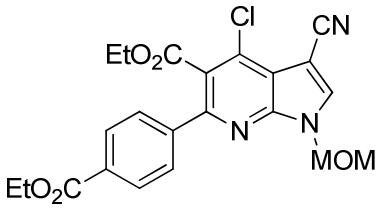
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.7, 166.5, 149.1, 147.2, 143.7, 138.5, 133.8, 132.1, 129.5, 129.3, 125.2, 123.8, 118.5, 116.3, 112.5, 109.3, 72.7, 62.3, 61.0, 57.1, 26.3, 14.2, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2991, 2987, 2925, 2904, 2227, 1730, 1713, 1626, 1608, 1594, 1525, 1471, 1458, 1437, 1427, 1421, 1400, 1390, 1366, 1336, 1291, 1254, 1243, 1197, 1175, 1137, 1116, 1110, 1060, 1032, 1015, 962, 937, 928, 921, 868, 857, 802, 775, 683, 668.

MS (EI, 70 eV) m/z (%): 515 (16) [M^+], 483 (15), 482 (16), 480 (40), 450 (21), 448 (27), 45 (100).

HRMS (EI): m/z calc. for [$C_{25}H_{23}Cl_2N_3O_5$] 515.1015, found: 510.1009.

Preparation of ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (37)



A microwave vial equipped with a stirring bar was charged with ethyl-2,4-dichloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**35b**; 1.05 g, 2.20 mmol, 1.0 equiv) in ethanol (32 mL). HCO_2NH_4 (416 mg, 6.60 mmol, 3.0 equiv) and Pd/C (99 mg, 0.04 mmol, 2 mol%) were added, the vial was sealed and the reaction mixture was heated using a *Biotage Initiator 2.5 system* (100 °C, 35 W, 1 h). The mixture was allowed to cool to room temperature, before another portion of Pd/C (99 mg, 0.04 mmol, 2 mol%) was added and the mixture was again exposed to microwave irradiation for 1 h. This cycle was repeated 2 h more (total reaction time: 4 h). After the last reaction cycle, the mixture was allowed to cool to ambient temperature and filtered through Celite®. After filtration, the solvent was removed *in vacuo*. Purification

of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 4:1) afforded **37** as colorless solid (738 mg, 76%).

mp.: 161.8 – 163.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, *J* = 8.3 Hz, 2H), 8.00 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 5.69 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

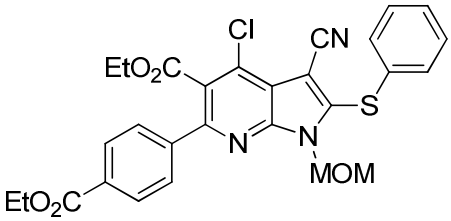
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.1, 166.0, 153.1, 146.7, 142.9, 137.5, 135.7, 131.1, 129.6, 128.6, 125.1, 116.2, 113.9, 86.9, 75.8, 62.4, 61.2, 57.4, 14.3, 13.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2229, 1732, 172, 1538, 1398, 1365, 1276, 1185, 1104, 1017, 918, 863, 770 719.

MS (EI, 70 eV) m/z (%): 441 (40) [M^+], 413 (27), 412 (43), 411 (71), 410 (83), 396 (23), 97 (12), 71 (11), 69 (11), 57 (16), 45 (100).

HRMS (EI): m/z calc. for [$C_{22}H_{20}ClN_3O_5$] 441.1091, found: 441.1091.

Preparation of ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-2-(phenylthio)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (4a)



Prepared according to **TP4** from ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**37**; 185 mg, 0.42 mmol, 1.0 equiv) in anhydrous THF (4 mL) and TMPMgCl·LiCl (1.175 M in THF, 0.46 mmol, 1.1 equiv) within 5 min at -30 °C. Subsequently, *S*-phenyl benzenesulfonothioate (**12j**; 136 mg, 0.55 mmol, 1.3 equiv) was added at the same temperature. Within 1 h, the reaction mixture was allowed to warm up to ambient temperature, quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 7:1) afforded **4a** as colorless solid (180 mg, 78%).

mp.: 111.2 – 113.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.11 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.44 (m, 2H), 7.38 – 7.34 (m, 3H), 5.80 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

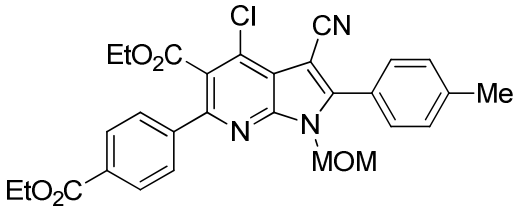
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.1, 165.8, 153.2, 147.6, 144.3, 142.8, 134.8, 131.4, 131.2, 131.1, 129.8, 129.6, 128.9, 128.6, 125.4, 116.6, 113.2, 93.3, 73.5, 62.5, 61.2, 57.4, 14.3, 13.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2923, 2229, 1739, 1708, 1538, 1439, 1393, 1281, 1246, 1201, 1182, 1116, 1108, 1017, 1000, 946, 922, 874, 833, 766, 755, 701, 653.

MS (EI, 70 eV) m/z (%): 549 (84) [M^+], 519 (24), 518 (13), 504 (13), 486 (16), 410 (15), 91 (14), 45 (100).

HRMS (EI): m/z calc. for [$C_{28}H_{24}ClN_3O_5S$] 549.1125, found: 549.1117.

Preparation of ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-2-(p-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (4b)



Prepared according to **TP4** from ethyl-4-chloro-3-cyano-6-(4-(ethoxycarbonyl)phenyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**37**; 221 mg, 0.50 mmol, 1.0 equiv) and TMPMgCl·LiCl (1.175 M in THF, 0.55 mmol, 1.1 equiv) within 5 min at -30 °C. Subsequently, $ZnCl_2$ (1 M in THF, 0.60 mmol, 1.2 equiv) was added and the mixture was allowed to warm to ambient temperature within 15 min. The generated organometallic was then added to a solution of 4-iodotoluene (**12k**; 163 mg, 0.75 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (17 mg, 0.02 mmol, 3 mol%) in THF (1 mL) and the suspension was stirred for 4 h at room temperature, quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **4b** as yellow oil (239 mg, 90%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.13 (d, *J* = 8.4 Hz, 2H), 7.74 (dd, *J* = 8.3, 3.9 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.60 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.52 (s, 3H), 2.46 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.2, 166.1, 152.5, 152.1, 147.7, 143.1, 141.7, 134.8, 130.9, 130.0, 130.0, 129.6, 128.6, 125.2, 124.1, 116.6, 115.1, 85.0, 73.6, 62.4, 61.2, 57.9, 21.6, 14.3, 13.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2985, 2931, 2220, 1730, 1718, 1610, 1541, 1492, 1464, 1450, 1422, 1406, 1363, 1307, 1290, 1267, 1248, 1222, 1203, 1192, 1174, 1122,

1093, 1057, 1013, 983, 978, 936, 922, 907, 871, 865, 853, 839, 831, 812, 801, 791, 782, 773, 767, 728, 720, 690, 661.

MS (EI, 70 eV) m/z (%): 531 (26) [M^+], 502 (12), 501 (12), 500 (39), 466 (14).

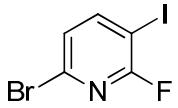
HRMS (EI): m/z calc. for [$C_{29}H_{26}ClN_3O_5$] 531.1561, found: 531.1555.

3. PREPARATION AND REACTIONS OF HETEROARYLMETHYLZINC REAGENTS

3.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources.

Preparation of 6-bromo-2-fluoro-3-iodopyridine



To a solution of 2-bromo-6-fluoropyridine (12.32 g, 70.0 mmol, 1.0 equiv) in anhydrous THF (70 mL) was added dropwise freshly prepared LDA (73.5 mmol, 1.1 equiv) at -78 °C and the reaction mixture was stirred at this temperature for 1 h.[222] Then, I_2 (17.77 g, 70.0 mmol, 1.0 equiv) dissolved in anhydrous THF (40 mL) was added and the reaction mixture was allowed to warm to -60 °C within 1.5 h. At this temperature, the reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 60:1) afforded 6-bromo-2-fluoro-3-iodopyridine as a colorless solid (17.33 g, 82%).

mp.: 67.3 – 74.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.96 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H).

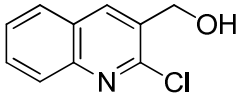
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.9 (d, *J* (C – F) = 242.2 Hz), 151.4 (d, *J* (C – F) = 2.9 Hz), 138.6 (d, *J* (C – F) = 12.4 Hz), 127.1 (d, *J* (C – F) = 5.3 Hz), 74.1 (d, *J* (C – F) = 41.4 Hz).

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1555, 1541, 1421, 1395, 1373, 1345, 1262, 1228, 1143, 1120, 1016, 1002, 886, 864, 823, 795, 728, 680.

MS (EI, 70 eV) m/z (%): 301 (100) [M^+], 221 (50), 95 (35).

HRMS (EI): m/z calc. for [C_5H_2BrFIN] 300.8399, found: 300.8378.

Preparation of (2-chloroquinolin-3-yl)methanol



Prepared according to the known literature procedure[223] from commercially available 2-chloro-3-formylquinoline (664 mg, 3.47 mmol, 1.0 equiv) and $NaBH_4$ (157 mg,

[222] The regioselective lithiation of 2-bromo-6-fluoropyridine proceeds analogously to the known lithiation of 2-chloro-6-fluoropyridine, see: Q. Zhou, B. B. Snider, *Org. Lett.* **2011**, *13*, 526.

[223] S. Kumar, D. Kaushik, S. Bawa, S. A. Khan, *Chem. Biol. Drug Des.* **2012**, *79*, 104.

4.16 mmol, 1.2 equiv) in anhydrous MeOH (20 mL). The reaction mixture was stirred for 1 h at 25 °C. The solvent was removed *in vacuo* and the residue was triturated with H_2O. Filtration afforded (2-chloroquinolin-3-yl)methanol as a beige solid (589 mg, 88%).

mp.: 164.7 – 166.3 °C.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.45 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.65 – 7.61 (m, 1H), 5.72 (t, *J* = 5.3 Hz, 1H), 4.68 (d, *J* = 4.6 Hz, 2H).

^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 148.4, 146.0, 135.9, 133.9, 130.1, 127.9, 127.5, 127.2, 127.2, 59.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3408, 3404, 3400, 3395, 3390, 3385, 3382, 3378, 3369, 3351, 3347, 3327, 3323, 3319, 2918, 2912, 2857, 1589, 1567, 1490, 1458, 1442, 1398, 1358, 1346, 1326, 1206, 1165, 1143, 1137, 1070, 1025, 1013, 989, 984, 961, 927, 906, 865, 804, 780, 761, 737, 672.

MS (EI, 70 eV) m/z (%): 195 (31), 193 (100) [M^+], 164 (57), 158 (58), 156 (49), 130 (33), 129 (51), 128 (87).

HRMS (EI): m/z calc. for [$C_{10}H_8ClNO$] 193.0294, found: 193.0294.

Preparation of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine

Prepared according to the known literature procedure[136] by adding a solution of Br_2 (16.0 g, 100 mmol, 1.0 equiv) in $CHCl_3$ (10 mL) to a solution of commercially available 7-azaindole (11.8 g, 100 mmol, 1.0 equiv) in $CHCl_3$ (250 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 x 500 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 5:1) afforded 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine as a yellowish solid (17.1 g, 87%).

mp: 163.1 – 165.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.91 (s, 1H), 8.35 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 (s, 1H), 7.23 (dd, *J* = 7.7, 4.9 Hz, 1H).

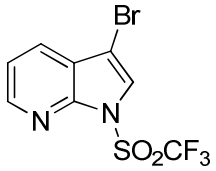
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 145.2, 141.0, 129.9, 125.7, 121.4, 116.2, 89.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1652, 1640, 1616, 1611, 1586, 1497, 1400, 1334, 1327, 1287, 1273, 1244, 1208, 1195, 1115, 1093, 1038, 980, 972, 963, 924, 895, 889, 800, 787, 763, 683, 674, 663.

MS (EI, 70 eV) m/z (%): 198 (100). 196 (97) [M^+], 117 (28), 116 (19), 90 (30), 63 (13).

HRMS (EI): m/z calc. for [$C_7H_5BrN_2$] 195.9636, found: 195.9631.

Preparation of 3-bromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine



To a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (28.8 g, 146 mmol, 1.0 equiv) in CH_2Cl_2 (500 mL) were added pyridine (18.85 mL, 234 mmol, 1.6 equiv) and trifluoromethanesulfonic anhydride (49.4 g, 175 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 40:1) afforded 3-bromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine as a colorless solid (32.2 g, 67%).

mp: 71.7 – 73.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.57 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.58 (s, 1H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1H).

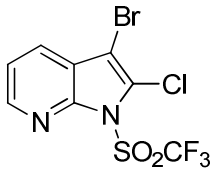
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.2, 147.1, 129.4, 125.0, 122.9, 121.1, 119.3 (q, *J* (C – F) = 323.4 Hz), 99.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3148, 3129, 1582, 1575, 1418, 1390, 1334, 1326, 1298, 1273, 1229, 1209, 1198, 1169, 1152, 1119, 1104, 1048, 1032, 983, 977, 937, 906, 898, 891, 886, 882, 865, 857, 801, 774, 764, 757, 722, 694, 688, 685, 680, 667.

MS (EI, 70 eV) m/z (%): 330 (49), 328 (49) [M^+], 266 (20), 264 (19), 197 (84), 195 (93), 116 (100).

HRMS (EI): m/z calc. for [$C_8H_4BrF_3N_2O_2S$] 327.9129, found: 327.9121.

Preparation of 3-bromo-2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine



To a solution of 3-bromo-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (30.9 g, 94 mmol, 1.0 equiv) in anhydrous THF (90 mL) was added TMPMgCl·LiCl (1.10 M in THF, 141 mmol, 1.5 equiv) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. Then, neat benzenesulfonyl chloride (20.0 g, 113 mmol, 1.2 equiv) was added and the reaction mixture was allowed to warm to room temperature, quenched with a sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded 3-bromo-2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine as an off-white solid (31.9 g, 93%).

mp: 89.7 – 91.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.53 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.42 (dd, *J* = 7.9, 4.9 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.6, 146.9, 128.4, 125.4, 121.8, 121.6, 119.2 (q, *J* (C – F) = 323.4 Hz), 101.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1734, 1580, 1535, 1475, 1432, 1413, 1391, 1370, 1365, 1333, 1309, 1305, 1257, 1245, 1222, 1208, 1188, 1167, 1134, 1109, 1092, 1078, 1073, 1068, 1054, 1044, 1016, 1008, 999, 996, 974, 945, 935, 931, 923, 906, 902, 898, 889, 883, 877, 873, 869, 866, 847, 795, 783, 771, 760, 745, 726, 706, 701, 689, 685, 680, 667.

MS (EI, 70 eV) m/z (%): 364 (32), 362 (23) [M^+], 300 (20), 298 (24), 231 (100), 229 (82), 152 (27), 150 (81), 109 (23), 887 (24).

HRMS (EI): m/z calc. for [$C_8H_3BrClF_3N_2O_2S$] 361.8739, found: 361.8730.

3.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Preparation of (dimethylamino)methyl heteroarenes of type 49

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with *N*,*N*,*N'*,*N'*-tetramethylmethanediamine (1.1 equiv) and anhydrous CH_2Cl_2

(1.0 M). At 0 °C neat trifluoroacetic anhydride (1.1 equiv) was added dropwise. After the highly exothermic reaction subsided and the smoke dissipated, the cooling was removed and the solution was allowed to warm up to 25 °C and stirred for 5 min. The solution of methylene(dimethyl)iminium trifluoroacetate was then cannulated dropwise at the indicated temperature to a solution of the organometallic reagent (**51**; 1.0 equiv). The reaction was found to be complete immediately after all of the solution had been transferred. The crude mixture was quenched with a sat. aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 2 (TP2): Preparation of heteroarylmethyl chlorides of type 48 from (dimethylamino)methyl heteroarenes of type 49

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with the (dimethylamino)methyl compound (**49**; 1.0 equiv) and anhydrous $CHCl_3$ (1.0 M). At 0 °C ethyl chloroformate (1.1 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 30 min. The mixture was then quenched with H_2O and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 3 (TP3): Preparation of heteroarylmethylzinc chlorides of type 53 by LiCl-promoted direct zinc insertion into heteroarylmethyl chlorides of type 48

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with LiCl (1.5 equiv). The flask was heated to 650 °C for 5 min under high vacuum using a heat gun. After cooling to 25 °C, the flask was flushed with argon and charged with Zn dust (1.5 equiv), followed by anhydrous THF (1.0 M). Neat 1,2-dibromoethane (5 mol%) was added and the resulting suspension was brought to reflux using a heat gun. After cooling to 25 °C, neat chlorotrimethylsilane (1 mol%) was added and the mixture was heated again to reflux using a heat gun. The suspension of the activated Zn dust was allowed to cool to 25 °C and then the heterobenzyl chloride (**48**; 1.0 equiv) was added as a 1.0 M solution in anhydrous THF. After the insertion reaction was finished (checked by GC analysis of hydrolyzed reaction aliquots), the *Schlenk*-flask was centrifuged for 30 min at 2000 rpm. The supernatant solution was cannulated into

another dry and argon flushed *Schlenk*-flask. The yield of the resulting heteroarylmethyl zinc chloride was determined by iodometric titration.[193]

Typical procedure 4 (TP4): *Negishi* cross-coupling reactions of heteroarylmethylzinc chlorides of type 53

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum was charged with the aryl or heteroaryl halide (0.9 equiv) and anhydrous THF (1.0 M). The appropriate Pd-catalyst and ligand were added and the reaction mixture was stirred at 25 °C for 5 min. At 0 °C the heteroarylmethylzinc chloride (**53**; 1.0 equiv) was added dropwise and the reaction mixture was allowed to warm up to 25 °C or heated to 50 °C. Stirring was continued for 16 h until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 5 (TP5): Addition reactions of heteroarylmethylzinc chlorides of type 53 to aldehydes and S-benzenesulfonothioates

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the aldehyde or the *S*-benzenesulfonothioate[197] (0.9 equiv) and anhydrous THF (1.0 M). The heteroarylmethylzinc chloride (**53**; 1.0 equiv) was added dropwise at 0 °C and the reaction mixture was allowed to warm to 25 °C or heated to 50 °C. Stirring was continued for 16 h until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 6 (TP6): Acylation reactions of heteroarylmethylzinc chlorides of type 53

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with CuCN·2LiCl (1.0 M solution in THF, 1.1 equiv) and cooled to –30 °C. The heteroarylmethylzinc zinc chloride (**53**; 1.0 equiv) was added dropwise at –30 °C and the mixture was stirred for 10 min. Then, the neat acid chloride (0.9 equiv) was added dropwise and the reaction mixture was allowed to slowly warm to room

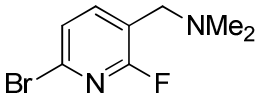
temperature. Stirring was continued for 16 h until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 7 (TP7): Allylation reactions of heteroarylmethylzinc chlorides of type 53

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the heteroarylmethylzinc chloride (**53**; 1.0 equiv) and cooled to –30 °C. CuCN·2LiCl (1.0 M solution in THF, 5 mol%) was added dropwise at –30 °C and the mixture was stirred for 10 min. Then, the neat allyl bromide (0.9 equiv) was added dropwise and the reaction mixture was allowed to slowly warm to room temperature. Stirring was continued for 16 h until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

3.3 PREPARATION OF (DIMETHYLAMINO)METHYL HETEROARENES

Preparation of 1-(6-bromo-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine (49a)



To a solution of 6-bromo-2-fluoro-3-iodopyridine (15.09g, 50.0 mmol, 1.0 equiv) in anhydrous THF (50 mL) was added dropwise *i*PrMgCl·LiCl (1.23 M in THF, 50.0 mmol, 1.0 equiv) at –30 °C and the reaction mixture was stirred at this temperature for 30 min. The generated organometallic **51a** was then reacted according to **TP1** at -30 °C. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 1:1) afforded **49a** as a yellowish oil (10.07 g, 86%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.68 (t, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 3.40 (s, 2H), 2.23 (s, 6H).

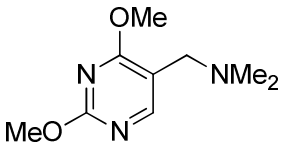
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.3 (d, *J* (C – F) = 246.4 Hz), 143.5 (d, *J* (C – F)= 5.3 Hz), 136.5 (d, *J* (C – F) = 13.9 Hz), 125.6 (d, *J* (C – F) = 5.0 Hz), 119.5 (d, *J* (C – F) = 27.4 Hz), 55.5 (d, *J* (C – F) = 2.5 Hz), 45.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2944, 2861, 2821, 2773, 1592, 1565, 1465, 1427, 1388, 1363, 1328, 1292, 1261, 1189, 1173, 1148, 1124, 1094, 1025, 964, 891, 852, 823, 795, 745, 737, 661.

MS (EI, 70 eV) m/z (%): 232 (25) [M$^+$], 190 (28), 188 (29), 109 (17), 58 (100).

HRMS (EI): m/z calc. for [$C_8H_{10}BrFN_2$] 232.0011, found: 232.0000.

Preparation of [(2,4-dimethoxypyrimidin-5-yl)methyl]dimethylamine (49c)



To a solution of 2,4-dimethoxy-5-bromo-pyrimidine[224] (4.82 g, 22.0 mmol, 1.0 equiv.) in anhydrous THF (22 mL) was added dropwise *i*PrMgCl·LiCl (1.34 M in THF, 24.2 mmol, 1.1 equiv) at –20 °C and the reaction mixture was stirred at this temperature for 2 h. The generated organometallic **51c** was then reacted according to **TP1** at -20 °C. Purification of the crude product by flash chromatography (Al_2O_3, Et_2O/ *i*-hexane = 4:1) afforded **49c** as a yellow oil (3.62 g, 83%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.97 (s, 1H), 3.85 (d, J = 5.0 Hz, 6H), 3.18 (s, 2H), 2.11 (s, 6H).

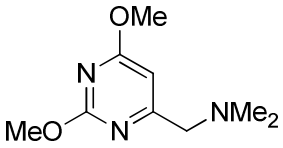
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.5, 164.5, 158.5, 111.4, 54.6, 54.4, 53.8, 44.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2974, 2945, 2899, 2858, 2817, 2767, 1678, 1600, 1565, 1454, 1395, 1383, 1359, 1330, 1290, 1236, 1198, 1175, 1143, 1096, 1071, 1055, 1016, 959, 936, 845, 822, 790, 762, 733.

MS (EI, 70 eV) m/z (%): 197 (73) [M$^+$], 153 (60), 153 (79), 153 (100), 153 (19), 123 (19), 96 (16), 58 (20), 55 (22), 42 (31).

HRMS (EI): m/z calc. for [$C_9H_{15}N_3O_2$] 197.1164, found: 197.1168.

Preparation of 1-(2,6-dimethoxypyrimidin-4-yl)-N,N-dimethylmethanamine (49d)



To a solution of 4-iodo-2,6-dimethoxypyrimidine[225] (266 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added dropwise *i*PrMgCl·LiCl (1.23 M in THF, 1.1 mmol, 1.1 equiv) at –40 °C and the reaction mixture was stirred at this temperature for 5 min.

[224] N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715.
[225] M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237.

The generated organometallic **51d** was then reacted according to **TP1** at -40 °C. Purification of the crude product by flash chromatography (Al_2O_3, *i*-hexane/ Et_2O = 2:1) afforded **49d** as a yellowish oil (156 mg, 79 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.49 (s, 1H), 3.94 (d, *J* = 5.8 Hz, 6H), 3.54 – 3.46 (m, 2H), 2.34 (s, 6H).

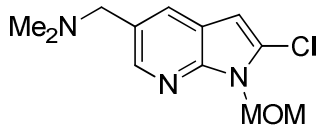
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.2, 169.1, 165.2, 100.0, 63.9, 54.7, 53.8, 45.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1591, 1563, 1478, 1455, 1377, 1347, 1283, 1251, 1201, 1098, 1043, 1029, 980, 942, 934, 923, 892, 857, 842, 812, 790, 776, 767, 759, 745, 725, 708, 690, 685, 677, 671, 662, 658, 652.

MS (EI, 70 eV) m/z (%): 196 (1) $[M-H]^+$, 155 (9), 154 (100).

HRMS (EI): m/z calc. for $[C_9H_{14}N_3O_2]$ 196.1086 $[M-H]^+$, found: 196.1068.

Preparation of 1-(2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*,*N*-dimethylmethanamine (49h)



To a solution of 5-bromo-2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**19**; 275 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (4 mL) was added dropwise *n*BuLi (2.61 M in THF, 1.0 mmol, 1.0 equiv) at –78 °C and the reaction mixture was stirred at this temperature for 10 min, before $MgCl_2$ (0.5 M in THF, 2.2 mL, 1.1 equiv) was added. The generated organometallic **51h** was then reacted according to **TP1** at -78 °C. Purification of the crude product by flash chromatography (Al_2O_3, *i*-hexane/Et_2O = 5:1) afforded **49h** as a brownish oil (121 mg, 48 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.21 (d, *J* = 1.5 Hz, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 6.42 (s, 1H), 5.68 (s, 2H), 3.50 (s, 2H), 3.35 (s, 3H), 2.24 (s, 6H).

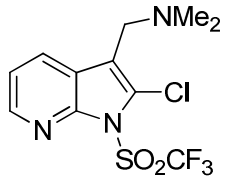
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.3, 144.4, 128.4, 127.7, 127.3, 119.8, 99.7, 72.1, 61.8, 56.7, 45.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2940, 2818, 2770, 1714, 1571, 1513, 1473, 1394, 1250, 1168, 1085, 1041, 914, 739.

MS (EI, 70 eV) m/z (%): 253 (54) $[M^+]$, 222 (26), 209 (89), 179 (100), 58 (48), 45 (73).

HRMS (EI): m/z calc. for $[C_{12}H_{16}ClN_3O]$ 253.0982, found: 253.0976.

Preparation of 1-(2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylmethanamine (49i)



To a solution of 3-bromo-2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (31.3 g, 86 mmol, 1.0 equiv) in anhydrous THF (160 mL) was added *i*PrMgCl·LiCl (1.23 M in THF, 94.6 mmol, 1.1 equiv) at -78 °C and the reaction mixture was stirred at this temperature for 5 min. The generated organometallic **51i** was then reacted according to **TP1** at -78 °C. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 5:1, 2% triethylamine) afforded **49i** as a slightly orange solid (25.9 g, 88%).

mp: 77.2 – 79.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.12 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.60 (s, 2H), 2.28 (s, 6H).

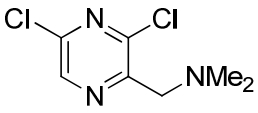
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.8, 145.9, 129.2, 124.5, 122.1, 121.2, 119.4 (q, *J* (C – F) = 323.8 Hz), 118.4, 53.3, 45.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2977, 2945, 2863, 2819, 2768, 1600, 1566, 1468, 1456, 1446, 1434, 1412, 1397, 1355, 1272, 1260, 1249, 1241, 1210, 1179, 1166, 1148, 1121, 1100, 1042, 1026, 1004, 991, 970, 954, 939, 911, 906, 893, 888, 884, 877, 872, 869, 865, 850, 822, 811, 790, 771, 739, 735, 731, 728, 725, 719, 713, 684, 669, 664, 656.

MS (EI, 70 eV) m/z (%): 341 (58) [M^+], 297 (45), 235 (32), 233 (100), 208 (27), 165 (51), 164 (35), 129 (30), 103 (31), 102 (42).

HRMS (EI): m/z calc. for [$C_{11}H_{11}ClF_3N_3O_2S$] 341.0213, found: 341.0211.

Preparation of 1-(3,5-dichloropyrazin-2-yl)-*N*,*N*-dimethylmethanamine (49j)



To a solution of 3,5-dichloro-2-iodopyrazine[64a] (2.75 g, 10.0 mmol, 1.0 equiv) in anhydrous THF (20 mL) was added dropwise *i*PrMgCl·LiCl (1.23 M in THF, 11.0 mmol, 1.1 equiv) at –78 °C and the reaction mixture was stirred at this temperature for 5 min, before $ZnCl_2$ (1.0 M in THF, 12.0 mL, 1.2 equiv) was added. The generated organometallic **51j** was then reacted according to **TP1** at -30 °C. Purification of the crude

product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 2:1) afforded **49j** as an orange oil (1.05 g, 51 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.49 (s, 1H), 3.71 (s, 2H). 2.34 (s, 6H).

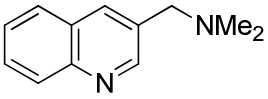
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 150.5, 147.3, 145.7, 141.8, 60.7, 45.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2944, 2821, 2772, 1535, 1515, 1465, 1454, 1420, 1360, 1320, 1277, 1259, 1243, 1182, 1152, 1129, 1097, 1078, 1042, 1027, 961, 900, 887, 847, 782, 727.

MS (EI, 70 eV) m/z (%): 205 (1) [M^+], 164 (24), 162 (37), 58 (100).

HRMS (EI): m/z calc. for [$C_7H_9Cl_2N_3$] 205.0174, found: 205.0128.

Preparation of *N*,*N*-dimethyl-1-(quinolin-3-yl)methanamine (49k)



To a solution of BuMgCl (1.50 M in THF, 18.5 mmol, 0.37 equiv) in anhydrous THF (50 mL) was added dropwise *n*BuLi (2.42 M in hexane, 38.0 mmol, 0.76 equiv) at –10 °C and the reaction mixture was stirred at this temperature for 1 h. Then, a solution of 3-bromoquinoline (10.4 g, 50.0 mmol, 1.0 equiv) in anhydrous THF (50 mL) was added at -30 °C and the resulting mixture was allowed to stir at -10 °C for 30 min.[226] The generated organometallic **51k** was then reacted according to **TP1** at -10 °C. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 2:1, 2% triethylamine) afforded **49k** as a yellow oil (2.32 g, 70%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.84 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 1.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.53 – 7.48 (m, 1H), 3.58 (s, 2H), 2.26 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 151.9, 147.5, 135.6, 131.5, 129.1, 129.1, 127.9, 127.6, 126.6, 61.6, 45.3.

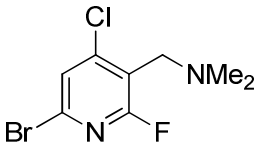
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2972, 2941, 2907, 2899, 2858, 2817, 2768, 1623, 1570, 1496, 1455, 1441, 1418, 1381, 1356, 1329, 1261, 1229, 1204, 1200, 1167, 1148, 1124, 1096, 1029, 994, 968, 957, 909, 892, 862, 837, 815, 786, 770, 751, 702, 690, 685, 679, 675, 670, 667, 664, 660, 657.

MS (EI, 70 eV) m/z (%): 186 (74) [M^+], 185 (33), 143 (27), 142 (53), 115 (44), 89 (14), 58 (100).

HRMS (EI): m/z calc. for [$C_{12}H_{14}N_2$] 186.1157, found: 186.1145.

[226] S. Dumouchel, F. Mongin, F. Trécourt, G. Quéguiner, *Tetrahedron* **2003**, *59*, 8629.

Preparation of 1-(6-bromo-4-chloro-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine (49l)



To a solution of 1-(6-bromo-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine (**49a**, 5.80 g, 25.0 mmol, 1.0 equiv) in anhydrous THF (25 mL) was added dropwise TMPMgCl·LiCl (1.18 M in THF, 30.0 mmol, 1.2 equiv) at –20 °C and the reaction mixture was stirred at this temperature for 1 h. Neat benzenesulfonyl chloride (4.64 g, 26.3 mmol, 1.05 equiv) was then slowly added and the mixture was allowed to warm to 0 °C within 1.5 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 5:1) afforded **49l** as a orange solid (4.86 g, 73%).

mp: 36.8 – 39.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45 (s, 1H), 3.53 (s, 2H), 2.29 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.3 (d, *J* (C – F) = 247.1 Hz), 149.7 (d, *J* (C – F) = 6.8 Hz), 137.1 (d, *J* (C – F) = 17.0 Hz), 126.5 (d, *J* (C – F) = 5.4 Hz), 118.3 (d, *J* (C – F) = 31.1 Hz), 52.9 (d, *J* (C – F) = 2.8 Hz), 45.3.

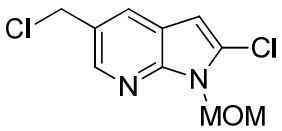
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2978, 2943, 2862, 2838, 2824, 2787, 2776, 1576, 1552, 1529, 1456, 1440, 1423, 1405, 1372, 1364, 1318, 1297, 1252, 1225, 1203, 1192, 1166, 1146, 1105, 1092, 1038, 1017, 986, 902, 845, 771, 762, 736, 719, 692, 688, 676, 668, 660, 656.

MS (EI, 70 eV) m/z (%): 266 (17) [M^+], 265 (14), 224 (35), 222 (26), 58 (100).

HRMS (EI): m/z calc. for [$C_8H_9BrClFN_2$] 265.9622, found: 265.9609.

3.4 PREPARATION OF CHLOROMETHYL HETEROARENES

Preparation of 2-chloro-5-(chloromethyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (48f)



Prepared according to **TP2** from 1-(2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*,*N*-dimethylmethanamine (**49h**; 254 mg, 1.0 mmol, 1.0 equiv) and ethyl

chloroformate (130 mg, 1.2 mmol, 1.2 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 85:15) afforded **48f** as a colorless solid (145 mg, 59%).

mp: 106 – 108 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.31 (d, *J* = 1.7 Hz, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 6.46 (s, 1H), 5.68 (s, 2H), 4.69 (s, 2H), 3.34 (s, 3H).

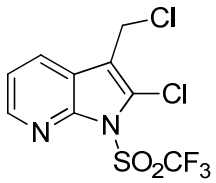
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.5, 143.7, 128.2, 128.0, 127.0, 119.7, 99.9, 72.2, 56.7, 44.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2934, 1571, 1514, 1474, 1395, 1377, 1307, 1280, 1258, 1170, 1108, 1080, 1028, 910, 722, 689.

MS (EI, 70 eV) m/z (%): 244 (11) [M^+], 214 (10), 179 (27), 45 (63), 43 (100).

HRMS (EI): m/z calc. for [$C_{10}H_{10}Cl_2N_2O$] 244.0170, found: 244.0167.

Preparation of 2-chloro-3-(chloromethyl)-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (48g)



Prepared according to **TP2** from 1-(2-chloro-1-((trifluoromethyl)sulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylmethanamine (**49i**; 25.9 g, 75.9 mmol, 1.0 equiv) and ethyl chloroformate (12.4 g, 113 mmol, 1.5 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **48g** as a colorless solid (18.6 g, 73%).

mp: 124.0 – 125.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.53 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.74 (s, 2H).

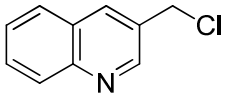
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.6, 146.4, 128.1, 125.3, 121.4, 120.3, 119.2 (q, *J* (C – F) = 323.6 Hz), 117.2, 34.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1597, 1562, 1477, 1439, 1425, 1409, 1395, 1368, 1283, 1277, 1259, 1249, 1212, 1173, 1164, 1149, 1121, 1104, 1087, 1047, 1030, 1016, 999, 977, 928, 906, 889, 880, 871, 862, 844, 833, 825, 818, 790, 766, 734, 714, 690, 685, 680, 674, 661.

MS (EI, 70 eV) m/z (%): 332 (34) [M^+], 299 (31), 297 (85), 233 (76), 164 (36), 138 (60), 103 (42), 102 (100), 76 (41).

HRMS (EI): m/z calc. for [$C_9H_5Cl_2F_3N_2O_2{}^{32}S$] 331.9401, found: 331.9400.

Preparation of 3-(chloromethyl)quinoline (48h)



Prepared according to **TP2** from *N*,*N*-dimethyl-1-(quinolin-3-yl)methanamine (**49k**; 25.8 mmol, 1.0 equiv) and ethyl chloroformate (4.21 g, 38.8 mmol, 1.5 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **48h** as a yellowish solid (2.74 g, 60%).

mp: 100.8 – 102.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.92 (d, *J* = 2.2 Hz, 1H), 8.14 – 8.09 (m, 2H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.58 – 7.53 (m, 1H), 4.76 (s, 2H).

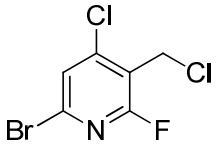
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 150.7, 147.7, 135.4, 130.3, 130.0, 129.3, 127.8, 127.5, 127.2, 43.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3060, 2959, 2922, 1618, 1605, 1571, 1526, 1495, 1464, 1437, 1419, 1378, 1373, 1356, 1340, 1280, 1271, 1259, 1232, 1207, 1178, 1154, 1124, 1015, 984, 959, 950, 932, 910, 876, 870, 865, 786, 768, 752, 722, 698, 667.

MS (EI, 70 eV) m/z (%): 177 (29) [M^+], 142 (100), 115 (24).

HRMS (EI): m/z calc. for [$C_{10}H_8ClN$] 177.0345, found: 177.0330.

Preparation of 6-bromo-4-chloro-3-(chloromethyl)-2-fluoropyridine (48i)



Prepared according to **TP2** from 1-(6-bromo-4-chloro-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine (**49l**; 4.82 g, 18.0 mmol, 1.0 equiv) and ethyl chloroformate (2.93 g, 27.0 mmol, 1.5 equiv) at 70 °C for 2 h. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 60:1) afforded **48i** as a colorless oil (3.11 g, 67%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.49 (s, 1H), 4.65 (s, 2H).

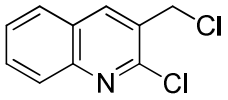
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.2 (d, *J* (C – F) = 249.3 Hz), 148.7 (d, *J* (C – F) = 5.6 Hz), 138.8 (d, *J* (C – F) = 16.9 Hz), 126.7 (d, *J* (C – F) = 5.6 Hz), 117.8 (d, *J* (C – F) = 31.0 Hz), 35.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1579, 1550, 1432, 1418, 1375, 1279, 1232, 1195, 1161, 1095, 958, 885, 854, 832, 773, 724, 687.

MS (EI, 70 eV) m/z (%): 259 (16), 257 (7) [M^+], 226 (24), 224 (100), 222 (67), 143 (13), 108 (12).

HRMS (EI): m/z calc. for [$C_6H_3BrCl_2FN$] 256.8810, found: 256.8808.

Preparation of 2-chloro-3-(chloromethyl)quinoline (48n)



Prepared according to the known literature procedure[223] from (2-chloroquinolin-3-yl)methanol (581 mg, 3.0 mmol, 1.0 equiv) and thionyl chloride (464 mg, 3.9 mmol, 1.3 equiv) in anhydrous benzene (10 mL). The reaction mixture was stirred for 4 h at 90 °C. After cooling to room temperature, the mixture was quenched with a sat. aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Recrystallization from *n*-heptane afforded **48n** as an off-colorless solid (519 mg, 82%).

mp: 118.7 – 120.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.26 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 4.82 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.6, 147.3, 138.7, 131.0, 129.0, 128.3, 127.6, 127.5, 127.1, 43.1.

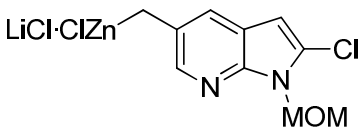
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1621, 1589, 1563, 1489, 1456, 1439, 1407, 1401, 1390, 1379, 1333, 1264, 1221, 1188, 1161, 1137, 1132, 1045, 1017, 987, 955, 934, 923, 886, 863, 801, 779, 757, 733, 721, 658.

MS (EI, 70 eV) m/z (%): 211 (22) [M^+], 178 (38), 176 (100), 140 (52).

HRMS (EI): m/z calc. for [$C_{10}H_7Cl_2N$] 210.9956, found: 210.9935.

3.5 PREPARATION OF HETEROARYLMETHYLZINC REAGENTS

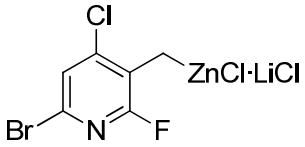
Preparation of ((2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)zinc chloride (53g)



Prepared according to **TP3** from 2-chloro-5-(chloromethyl)-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**48f**; 980 mg, 4.0 mmol, 1.0 equiv), Zn dust (392 mg, 6.0 mmol,

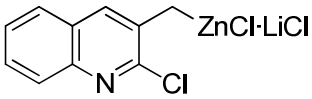
1.5 equiv) and LiCl (254 mg, 6.0 mmol, 1.5 equiv). Reaction time: 2.5 h at 50 °C. Iodometric titration of the filtrated solution indicated a yield of 60%.

Preparation of (6-bromo-4-chloro-2-fluoropyridin-3-yl)methylzinc chloride (53h)



Prepared according to **TP3** from 6-bromo-4-chloro-3-(chloromethyl)-2-fluoropyridine (**48i**; 2.05 g, 7.9 mmol, 1.0 equiv), Zn dust (776 mg, 11.9 mmol, 1.5 equiv) and LiCl (504 mg, 11.9 mmol, 1.5 equiv). Reaction time: 1 h at 25 °C. Iodometric titration of the centrifugated solution indicated a yield of 90%.

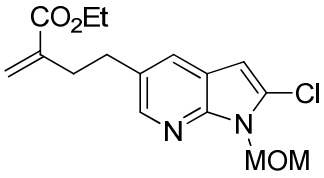
Preparation of ((2-chloroquinolin-3-yl)methyl)zinc chloride (53i)



Prepared according to **TP3** from 2-chloro-3-(chloromethyl)quinoline (**48n**; 2.12 g, 10.0 mmol, 1.0 equiv), Zn dust (981 mg, 15.0 mmol, 1.5 equiv) and LiCl (636 mg, 15.0 mmol, 1.5 equiv). Reaction time: 1 h at 25 °C. Iodometric titration of the filtrated solution indicated a yield of 78%.

3.6 REACTIONS OF HETEROARYLMETHYLZINC REAGENTS WITH ELECTROPHILES

Preparation of ethyl 4-(2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-methylenebutanoate (54g)



Prepared according to **TP6** from ((2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)zinc chloride (**53g**; 1.0 mmol, 1.0 equiv) and ethyl (2-bromomethyl)acrylate (**57f**; 174 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1 then 7:1) afforded **54g** as a colorless oil (286 mg, 98 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 6.40 (s, 1H), 6.15 (d, *J* = 1.0 Hz, 1H), 5.66 (s, 2H), 5.47 (d, *J* = 1.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 3H), 2.87 (m, 2H), 2.63 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

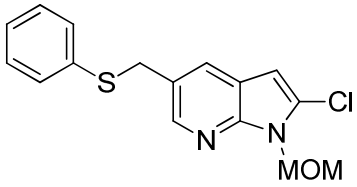
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.0, 146.6, 143.9, 139.7, 130.3, 127.3, 127.1, 125.5, 119.8, 99.4, 72.1, 60.7, 56.6, 34.5, 32.1, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 1712, 1631, 1473, 1394, 1276, 1183, 11112, 1086, 1030, 915, 755.

MS (EI, 70 eV) m/z (%): 322 (26) [M^+], 292 (18), 209 (100), 179 (62), 45 (47).

HRMS (EI): m/z calc. for [$C_{16}H_{19}ClN_2O_3$] 322.1084, found: 322.1079.

Preparation of 2-chloro-1-(methoxymethyl)-5-((phenylthio)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (54h)



Prepared according to **TP5** from ((2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)zinc chloride (**53g**; 1.0 mmol, 1.0 equiv) and *S*-phenyl benzenesulfonothioate (**57g**; 225 mg, 0.9 mmol, 0.9 equiv) at 50 °C. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **54h** as a colorless oil (232 mg, 81 %).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.21 (d, *J* = 1.7 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.33 – 7.16 (m, 5H), 6.41 (s, 1H), 5.67 (s, 2H), 4.19 (s, 2H), 3.35 (s, 3H).

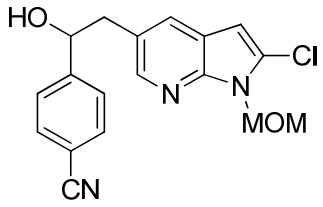
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.0, 143.8, 135.7, 130.2, 128.9, 127.8, 127.5, 126.8, 126.6, 119.7, 99.6, 72.1, 56.6, 36.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2933, 1571, 1513, 1472, 1394, 1377, 1304, 1278, 1111, 1084, 1042, 913, 734.

MS (EI, 70 eV) m/z (%): 318 (12) [M^+], 209 (100), 181 (16), 45 (34).

HRMS (EI): m/z calc. for [$C_{16}H_{15}ClN_2OS$] 318.0594, found: 318.0589.

Preparation of 4-(2-(2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-1-hydroxyethyl)benzonitrile (54i)



Prepared according to **TP5** from ((2-chloro-1-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)zinc chloride (**53g**; 1.0 mmol, 1.0 equiv) and 4-cyanobenzaldehyde (**57h**; 118 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 2:1, 2% triethylamine) afforded **54i** as a colorless solid (260 mg, 85%).

mp: 169.6 – 171.2 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ (ppm): 8.04 (d, *J* = 1.7 Hz, 1H), 7.76 – 7.74 (m, 3H), 7.50 (d, *J* = 8.2 Hz, 2H), 6.64 (s, 1H), 5.61 (d, *J* = 4.7 Hz, 1H), 5.57 (s, 2H), 4.91 – 4.87 (m, 1H), 3.21 (s, 3H), 3.04 – 2.99 (m, 1H), 2.94 (dd, *J* = 13.7, 7.7 Hz, 1H).

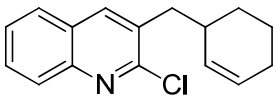
^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ (ppm): 151.1, 146.1, 144.6, 131.9, 128.7, 127.5, 126.9, 126.0, 119.0, 118.9, 109.5, 99.5, 72.9, 71.7, 56.0, 42.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3218, 2930, 2223, 1606, 1571, 1475, 1375, 1277, 1112, 1089, 1089, 1052, 908, 758.

MS (EI, 70 eV) m/z (%): 341 (9) [M^+], 310 (10), 209 (100), 179 (51), 45 (40).

HRMS (EI): m/z calc. for [$C_{18}H_{16}ClN_3O_2$] 341.0931, found: 341.0922.

Preparation of 2-chloro-3-(cyclohex-2-en-1-ylmethyl)quinoline (54j)



Prepared according to **TP7** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and 3-bromocyclohex-1-ene (**57i**; 145 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 40:1) afforded **54j** as a colorless solid (174 mg, 76%).

mp: 72.9 – 74.2 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.98 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.53 – 7.49 (m, 1H), 5.75-5.71 (m, 1H), 5.56 (dd, *J* = 10.1, 2.1 Hz, 1H), 2.90 – 2-77 (m, 2H), 2.62 – 2.56 (m, 1H), 2.00 (dd, *J* = 4.5, 2.2 Hz, 2H), 1.79 – 1.70 (m, 2H), 1.56 – 1.49 (m, 1H), 1.37 – 1.30 (m, 1H).

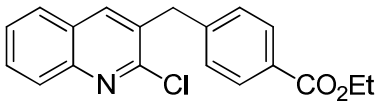
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 151.72, 146.42, 138.44, 132.41, 130.23, 129.63, 128.13, 128.05, 127.30, 126.96, 126.90, 39.87, 34.78, 28.77, 25.26, 21.06.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3011, 2941, 2927, 2911, 2880, 2870, 2828, 1591, 1564, 1485, 1449, 1435, 1429, 1402, 1380, 1337, 1200, 1152, 1131, 1077, 1050, 1038, 1013, 1005, 973, 970, 961, 948, 924, 918, 897, 859, 777, 760, 753, 746, 725, 718, 705, 699, 683, 670, 664.

MS (EI, 70 eV) m/z (%): 257 (4) [M^+], 177 (100), 140 (11).

HRMS (EI): m/z calc. for [$C_{16}H_{16}ClN$] 257.0971, found: 257.0973.

Preparation of ethyl 4-((2-chloroquinolin-3-yl)methyl)benzoate (54k)



Prepared according to **TP4** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (**57j**; 248 mg, 0.9 mmol, 0.9 equiv) at 50 °C. Catalyst system: Pd-PEPPSI-*i*Pr (34 mg, 5 mol%). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **54k** as a yellow solid (204 mg, 70%).

mp: 110.8 – 112.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.02 – 7.99 (m, 3H), 7.79 (s, 1H), 7.71 – 7.66 (m, 2H), 7.54 – 7.50 (m, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.27 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

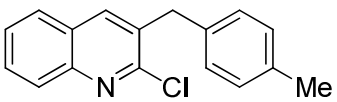
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.4, 151.3, 146.6, 143.3, 138.3, 132.2, 130.1, 130.0, 129.1, 129.1, 128.2, 127.3, 127.1, 127.1, 60.9, 39.1, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1705, 1591, 1563, 1489, 1395, 1373, 1336, 1328, 1308, 1302, 1276, 1249, 1202, 1175, 1165, 1140, 1135, 1124, 1107, 1099, 1026, 1017, 1014, 994, 960, 946, 937, 865, 856, 806, 775, 756, 749, 734, 728, 698, 679, 675, 657, 654.

MS (EI, 70 eV) m/z (%): 325 (76) [M^+], 280 (84), 252 (19), 217 (61), 216 (100).

HRMS (EI): m/z calc. for [$C_{19}H_{16}ClNO_2$] 325.0870, found: 325.0860.

Preparation of 2-chloro-3-(4-methylbenzyl)quinoline (54l)



Prepared according to **TP4** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and 1-iodo-4-methylbenzene (**57k**; 169 mg, 0.9 mmol, 0.9 equiv) at

50 °C. Catalyst system: Pd-PEPPSI-*i*Pr (34 mg, 5 mol%). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 100:1) afforded **54l** as a yellowish solid (116 mg, 48%).

mp: 91.6 – 93.5 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.00 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.70 – 7.64 (m, 2H), 7.51 – 7.47 (m, 1H), 7.16 – 7.11 (m, 4H), 4.18 (s, 2H), 2.35 (s, 3H).

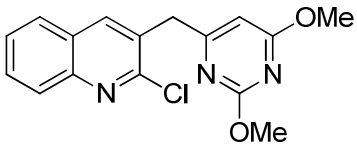
^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 151.5, 146.5, 138.0, 136.3, 134.9, 133.3, 129.8, 129.4, 129.0, 128.1, 127.4, 127.1, 126.9, 38.7, 21.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1618, 1589, 1563, 1514, 1487, 1452, 1419, 1401, 1378, 1332, 1323, 1311, 1303, 1213, 1203, 1183, 1173, 1135, 1115, 1103, 1028, 1014, 984, 968, 957, 946, 938, 886, 858, 848, 825, 814, 800, 777, 769, 757, 739, 728, 713, 709, 699, 685, 680, 675, 667, 660, 657, 654.

MS (EI, 70 eV) m/z (%): 269 (32), 267 (84) [M^+], 232 (53), 231 (100), 230 (50), 217 (37), 216 (71).

HRMS (EI): m/z calc. for [$C_{17}H_{14}ClN$] 267.0815, found: 267.0818.

Preparation of 2-chloro-3-((2,6-dimethoxypyrimidin-4-yl)methyl)quinoline (54m)



Prepared according to **TP4** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and 4-iodo-2,6-dimethoxypyrimidine (**57l**; 239 mg, 0.9 mmol, 0.9 equiv) at 50 °C. Catalyst system: Pd-PEPPSI-*i*Pr (34 mg, 5 mol%). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **54m** as a yellowish solid (154 mg, 49%).

mp: 128.8 – 130.6 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.06 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H) 7.71 – 7.67 (m, 1H), 7.55 – 7.51 (m, 1H), 6.21 (s, 1H), 4.20 (s, 2H), 3.93 (s, 3H), 3.93 (s, 3H).

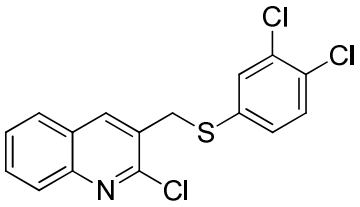
^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 172.2, 168.7, 165.4, 151.3, 146.8, 139.2, 130.2, 129.8, 128.2, 127.4, 127.2, 127.1, 100.5, 54.7, 53.8, 40.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1595, 1579, 1566, 1489, 1477, 1467, 1454, 1444, 1403, 1385, 1375, 1353, 1337, 1316, 1297, 1261, 1209, 1179, 1154, 1138, 1130, 1098, 1039, 1029, 1016, 981, 950, 939, 924, 890, 859, 848, 795, 774, 751, 717, 705, 680, 667.

MS (EI, 70 eV) m/z (%): 315 (1) [M^+], 281 (19), 280 (100), 208 (10).

HRMS (EI): m/z calc. for [$C_{16}H_{14}ClN_3O_2$] 315.0775, found: 315.0765.

Preparation of 2-chloro-3-(((3,4-dichlorophenyl)thio)methyl)quinoline (54n)



Prepared according to **TP5** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and *S*-(3,4-dichlorophenyl) benzenesulfonothioate[197] (**57m**; 287 mg, 0.9 mmol, 0.9 equiv) at 50 °C. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 40:1) afforded **54n** as a colorless solid (206 mg, 65%).

mp: 115.0 – 117.1 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.00 (d, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 7.73 – 7.69 (m, 2H), 7.56 – 7.52 (m, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.31 (s, 2H).

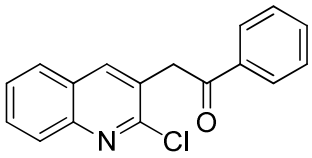
^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 150.4, 146.9, 138.1, 135.2, 133.0, 132.1, 131.4, 130.7, 130.6, 129.8, 128.6, 128.2, 127.4, 127.3, 127.0, 36.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1564, 1490, 1458, 1432, 1396, 1366, 1335, 1160, 1134, 1093, 1064, 1039, 1029, 961, 926, 912, 879, 869, 815, 807, 780, 761, 727, 716, 692, 676.

MS (EI, 70 eV) m/z (%): 353 (8) [M^+], 176 (100), 107 (28), 95 (27), 93 (32), 81 (33).

HRMS (EI): m/z calc. for [$C_{16}H_{10}Cl_3NS$] 352.9600, found: 352.9586.

Preparation of 2-(2-chloroquinolin-3-yl)-1-phenylethanone (54o)



Prepared according to **TP6** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 5.0 mmol, 1.0 equiv) and benzoyl chloride (**57n**; 562 mg, 4.0 mmol, 0.8 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1, 2% triethylamine) afforded **54o** as a colorless solid (747 mg, 66%).

mp.: 132.8 – 134.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09 – 7.93 (m, 4H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.52 (q, *J* = 7.3 Hz, 3H), 4.57 (s, 2H).

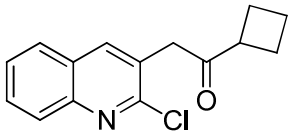
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 195.6, 151.2, 147.0, 139.7, 136.3, 133.6, 130.2, 128.8, 128.3, 128.3, 127.4, 127.3, 127.2, 127.1, 42.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2923, 1686, 1592, 1563, 1489, 1448, 1411, 1398, 1334, 1303, 1213, 1189, 1170, 1138, 1130, 1036, 978, 962, 929, 916, 891, 782, 758, 735, 691.

MS (EI, 70 eV) m/z (%): 281 (9) [M^+], 140 (13), 105 (100), 77 (27).

HRMS (EI): m/z calc. for [$C_{17}H_{12}ClNO$] 281.0607, found: 281.0597.

Preparation of 2-(2-chloroquinolin-3-yl)-1-cyclobutylethanone (54p)



Prepared according to **TP6** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 1.0 mmol, 1.0 equiv) and cyclobutanecarbonyl chloride (**57o**; 107 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1, 2% triethylamine) afforded **54p** as a yellowish solid (157 mg, 67%).

mp: 90.1 – 91.6 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.99 – 7.97 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.54 – 7.50 (m, 1H), 3.92 (s, 2H), 3.47 – 3.38 (m, 1H), 2.38 – 2.28 (m, 2H), 2.21 – 2.12 (m, 2H), 2.03 – 1.91 (m, 1H), 1.88 – 1.79 (m, 1H).

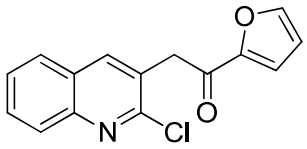
^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.8, 151.0, 146.9, 139.7, 130.2, 128.2, 127.3, 127.1, 127.1, 127.1, 45.5, 44.4, 24.4, 17.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2984, 2971, 2938, 2927, 2918, 2914, 2863, 1714, 1591, 1564, 1487, 1408, 1397, 1379, 1354, 1336, 1318, 1295, 1241, 1185, 1172, 1132, 1121, 1079, 1038, 1015, 991, 967, 925, 920, 881, 873, 860, 818, 794, 780, 764, 749, 737, 716, 700, 667.

MS (EI, 70 eV) m/z (%): 259 (2) [M^+], 179 (33), 177 (100), 140 (27), 83 (27).

HRMS (EI): m/z calc. for [$C_{15}H_{14}ClNO$] 259.0764, found: 259.0754.

Preparation of 2-(2-chloroquinolin-3-yl)-1-(furan-2-yl)ethanone (54q)



Prepared according to **TP6** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 2.0 mmol, 1.0 equiv) and furan-2-carbonyl chloride (**57p**; 222 mg, 1.7 mmol, 0.85 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1, 2% triethylamine) afforded **54q** as a yellow solid (285 mg, 62%).

mp: 117.5 – 119.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.08 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.64 (s, 1H), 7.54 (7, *J* = 7.5 Hz, 3H), 7.33 (d, *J* = 3.5 Hz, 1H), 6.59 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.44 (s, 2H).

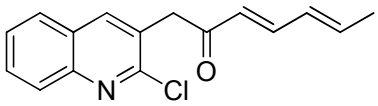
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 184.6, 152.2, 151.1, 146.9, 146.9, 139.9, 130.3, 128.2, 127.3, 127.2, 126.6, 118.0, 112.6, 42.5. (One signal not observed; possible coincidental isochronicity.)

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1673, 1616, 1593, 1562, 1490, 1463, 1409, 1394, 1338, 1258, 1238, 1217, 1190, 1179, 1175, 1159, 1153, 1139, 1133, 1078, 1035, 1013, 996, 971, 964, 937, 920, 908, 898, 890, 881, 873, 869, 856, 819, 791, 779, 768, 761, 728, 717, 693, 685, 680, 677, 667, 663, 659, 656.

MS (EI, 70 eV) m/z (%): 271 (2) [M^+], 236 (83), 176 (17), 140 (45), 95 (100).

HRMS (EI): m/z calc. for [$C_{15}H_{10}ClNO_2$] 271.0400, found: 271.0399.

Preparation of (3*E*,5*E*)-1-(2-chloroquinolin-3-yl)hepta-3,5-dien-2-one (54r)



Prepared according to **TP6** from ((2-chloroquinolin-3-yl)methyl)zinc chloride (**53i**; 2.0 mmol, 1.0 equiv) and (2*E*,4*E*)-hexa-2,4-dienoyl chloride (**57q**; 222 mg, 1.7 mmol, 0.85 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1, 2% triethylamine) afforded **54r** as a yellow solid (256 mg, 55%).

mp: 107.3 – 109.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.99 (d, *J* = 8.6 Hz, 2H), 7.75 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.54 – 7.49 (m, 1H), 7.33 – 7.24 (m, 1H), 6.24 – 6.16 (m, 3H), 4.11 (s, 2H), 1.86 (d, *J* = 5.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 195.7, 151.2, 146.8, 144.4, 141.8, 139.6, 130.2, 130.1, 128.2, 127.4, 127.3, 127.2, 127.1, 126.4, 44.8, 18.9.

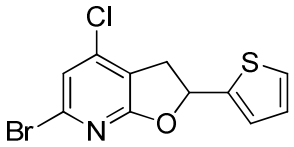
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1681, 1633, 1623, 1616, 1592, 1569, 1563, 1489, 1404, 1394, 1372, 1338, 1293, 1273, 1260, 1228, 1212, 1203, 1200, 1185, 1162, 1140, 1126, 1099, 1071, 1037, 1013, 995, 967, 961, 946, 937, 922, 888, 858, 841, 835, 832, 825, 818, 809, 783, 767, 758, 749, 720, 711, 690, 685, 680, 674, 667, 663.

MS (EI, 70 eV) m/z (%): 271 (4) [M$^+$], 176 (21), 140 (36), 96 (21), 95 (88), 67 (100).

HRMS (EI): m/z calc. for [$C_{16}H_{14}ClNO$] 271.0764, found: 271.0752.

3.7 PREPARATION OF HIGHLY FUNCTIONALIZED ANNULATED HETEROCYCLES

Preparation of 6-bromo-4-chloro-2-(thiophen-2-yl)-2,3-dihydrofuro[2,3-*b*]pyridine (59b)



Prepared according to **TP5** from (6-bromo-4-chloro-2-fluoropyridin-3-yl)methylzinc chloride (**53h**; 1.0 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (**57r**; 90 mg, 0.8 mmol, 0.8 equiv) at 50 °C for 2 h. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 4:1) afforded **59b** as a yellow solid (174 mg, 69%).

mp: 78.3– 81.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.33 (dd, *J* = 5.0, 0.7 Hz, 1H), 7.12 (d, *J* = 3.4 Hz, 1H), 7.07 (s, 1H), 7.00 (dd, *J* = 4.9, 3.7 Hz, 1H), 6.11 (dd, *J* = 9.3, 7.4 Hz, 1H), 3.67 (dd, *J* = 16.8, 9.4 Hz, 1H), 3.36 (dd, *J* = 16.8, 7.3 Hz, 1H).

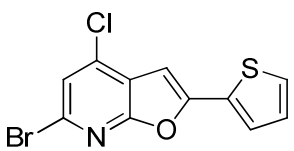
^{13}C-NMR (CDCl$_3$, 75 MHz) δ (ppm): 167.1, 142.3, 141.9, 139.2, 127.0, 126.4, 125.8, 120.6, 117.4, 79.0, 35.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1588, 1564, 1409, 1377, 1316, 1303, 1247, 1243, 1099, 956, 945, 887, 847, 837, 821, 736, 717, 711, 701, 656.

MS (EI, 70 eV) m/z (%): 317 (100), 315 (74) [M$^+$], 236 (37), 173 (35), 172 (47).

HRMS (EI): m/z calc. for [$C_{11}H_7BrClNOS$] 314.9120, found: 314.9104.

Preparation of 6-bromo-4-chloro-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (58b)



To a solution of 6-bromo-4-chloro-2-(thiophen-2-yl)-2,3-dihydrofuro[2,3-*b*]pyridine (**59b**, 678 mg, 2.1 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (4 mL) was added 2,3-

dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.46 g, 6.4 mmol, 3.0 equiv) and the reaction mixture was stirred under reflux for 3 h. The reaction mixture was quenched with a sat. aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 20:1) afforded **58b** as a yellowish solid (470 mg, 70%).

mp: 131.1 – 133.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.56 (d, *J* = 3.6, 1H), 7.44 – 7.41 (m, 2H), 7.12 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.85 (s, 1H).

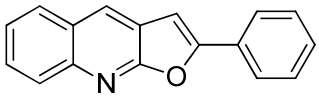
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.1, 151.9, 137.0, 134.5, 131.2, 128.3, 127.9, 126.6, 123.4, 120.4, 97.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1595, 1576, 1563, 1495, 1428, 1414, 1356, 1331, 1320, 1290, 1268, 1203, 1097, 1087, 1048, 990, 963, 900, 861, 846, 838, 786, 750, 725, 718, 702, 666, 654.

MS (EI, 70 eV) m/z (%): 315 (100), 314 (16), 313 (70) [M^+], 205 (20), 170 (11).

HRMS (EI): m/z calc. for [$C_{11}H_5BrClNOS$] 312.8964, found: 312.8955.

Preparation of 2-phenylfuro[2,3-*b*]quinoline (60a)



Prepared analogously to the known literature procedure[201] from 2-(2-chloroquinolin-3-yl)-1-phenylethanone (**54o**; 141 mg, 0.5 mmol, 1.0 equiv), tripotassium phosphate (212 mg, 1.0 mmol, 2.0 equiv) and *N*,*N*'-dimethylethylenediamine (DMEDA, 13 mg, 30 mol%) in anhydrous DMF (2 mL). The reaction mixture was stirred for 4 h at 105 °C. After cooling to room temperature, the mixture was quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **60ab** as an off-white solid (75 mg, 62%).

mp: 194.0 – 196.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.26 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.93 (m, 2H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.38 (m, 4H), 7.07 (s, 1H).

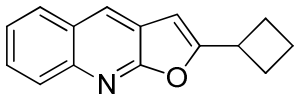
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.6, 157.7, 144.7, 129.7, 129.3, 128.9, 128.7, 128.4, 128.2, 127.7, 126.7, 125.4, 124.8, 122.1, 99.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3053, 2921, 2852, 1616, 1605, 1585, 1564, 1487, 1467, 1445, 1389, 1350, 1333, 1327, 1280, 1264, 1243, 1182, 1161, 1147, 1138, 1107, 1099, 1072, 1035, 1019, 1015, 980, 952, 935, 916, 902, 898, 864, 850, 806, 781, 758, 750, 730, 686, 677, 654.

MS (EI, 70 eV) m/z (%): 245 (100) [M^+], 217 (16), 216 (20).

HRMS (EI): m/z calc. for [$C_{17}H_{11}NO$] 245.0841, found: 245.0833.

Preparation of 2-cyclobutylfuro[2,3-*b*]quinoline (60b)



Prepared analogously to the known literature procedure[201] from 2-(2-chloroquinolin-3-yl)-1-cyclobutylethanone (**54p**; 130 mg, 0.5 mmol, 1.0 equiv), tripotassium phosphate (212 mg, 1.0 mmol, 2.0 equiv) and DMEDA (13 mg, 30 mol%) in anhydrous DMF (2 mL). The reaction mixture was stirred for 4 h at 105 °C. After cooling to room temperature, the mixture was quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **60b** as a yellowish solid (73 mg, 65%).

mp: 92.7 – 94.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.17 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 3.75 – 3.63 (m, 1H), 2.47 – 2.38 (m, 4H), 2.16 – 1.95 (m, 2H).

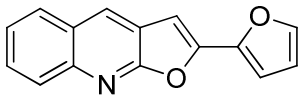
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 164.6, 161.8, 144.2, 128.4, 128.2, 127.6, 127.4, 126.5, 124.5, 122.0, 99.4, 34.0, 27.3, 18.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2985, 2977, 2956, 2938, 2927, 2857, 1612, 1593, 1588, 1505, 1466, 1443, 1391, 1357, 1351, 1328, 1244, 1230, 1218, 1192, 1182, 1152, 1137, 1102, 1046, 1027, 1018, 1001, 974, 947, 923, 908, 886, 868, 855, 800, 781, 773, 749, 732, 711, 692, 682, 679, 675, 671, 667, 660, 656.

MS (EI, 70 eV) m/z (%): 223 (14) [M^+], 196 (15), 195 (100), 167 (13).

HRMS (EI): m/z calc. for [$C_{15}H_{13}NO$] 223.0997, found: 223.0996.

Preparation of 2-(furan-2-yl)furo[2,3-*b*]quinoline (60c)



Prepared analogously to the known literature procedure[201] from 2-(2-chloroquinolin-3-yl)-1-(furan-2-yl)ethanone (**54q**; 136 mg, 0.5 mmol, 1.0 equiv), tripotassium phosphate (212 mg, 1.0 mmol, 2.0 equiv) and DMEDA (13 mg, 30 mol%) in anhydrous DMF (2 mL). The reaction mixture was stirred for 3 h at 105 °C. After cooling to room temperature, the mixture was quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **60c** as an off-white solid (64 mg, 54%).

mp: 157.6 – 159.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.25 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.55 (d, *J* = 1.1 Hz, 1H), 7.51 – 7.46 (m, 1H), 6.99 (d, *J* = 3.4 Hz, 1H), 6.94 (s, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.3, 149.5, 145.3, 144.7, 144.3, 128.7, 128.4, 128.2, 127.7, 126.8, 124.9, 121.6, 112.1, 110.3, 98.9.

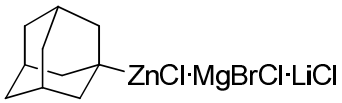
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3126, 3106, 2922, 1637, 1616, 1585, 1532, 1504, 1475, 1454, 1389, 1350, 1326, 1247, 1236, 1227, 1210, 1184, 1163, 1155, 1145, 1107, 1071, 1058, 1010, 986, 952, 938, 907, 902, 891, 881, 863, 855, 838, 807, 778, 769, 753, 745, 732, 681, 667, 662.

MS (EI, 70 eV) m/z (%): 236 (17), 235 (100) [M^+],179 (17), 178 (22).

HRMS (EI): m/z calc. for [$C_{15}H_9NO_2$] 235.0633, found: 235.0627.

3.8 APPLICATION TO THE SYNTHESIS OF A BIOLOGICALLY ACTIVE COMPOUND

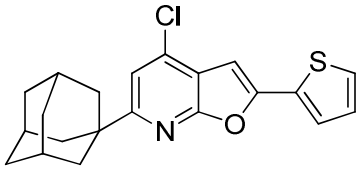
Preparation of adamantan-1-zinc chloride (64)



Prepared according to the known literature procedure.[206] A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (233 mg, 5.5 mmol, 1.1 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (241 mg, 10.0 mmol, 2.0 equiv) were added, followed by anhydrous THF (5 mL). The magnesium was activated using 1,2-dibromoethane (47 mg, 0.25 mmol, 5 mol%) and TMSCl (16 mg, 0.15 mmol,

3 mol%). Then, a $ZnCl_2$-solution (5.5 mL, 1.0 M in THF, 1.1 equiv) was added followed by 1-bromoadamantane (1.08 g, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at 25 °C for 2 h. Iodometric titration of the centrifugated solution indicated a yield of 85%.[193]

Preparation of 6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-4-chloro-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (65)



To a solution of the adamantly zinc reagent (**64**, 2.0 mmol, 1.0 equiv) in anhydrous THF (2 mL), were added $Pd(OAc)_2$ (9 mg, 0.04 mmol, 2 mol%), SPhos (33 mg, 0.08 mmol, 4 mol%) and 6-bromo-4-chloro-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (**58b;** 564 mg, 1.8 mmol, 0.9 equiv), and the resulting mixture was stirred for 1 h at 60 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacou*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 60:1) afforded **65** as a yellowish solid (444 mg, 67%).

mp: 176.9 – 179.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.58 (dd, *J* = 3.6, 0.8 Hz, 1H), 738 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.21 (s, 1H), 7.10 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.86 (s, 1H), 2.13 – 1.79 (m, 15H).

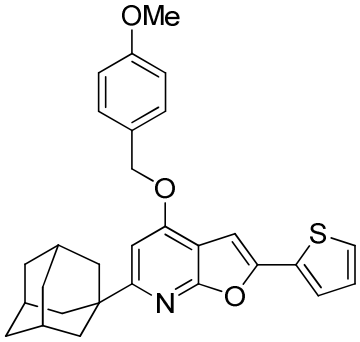
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.5, 161.4, 150.9, 136.0, 132.2, 128.1, 126.9, 125.9, 118.5, 115.7, 98.0, 42.1, 39.3, 36.7, 28.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2903, 2847, 1574, 1451, 1421, 1348, 1316, 1303, 1254, 1232, 1221, 1206, 1164, 1140, 1105, 1078, 1050, 1044, 1002, 986, 978, 963, 907, 878, 856, 849, 838, 831, 817, 790, 777, 760, 747, 730, 699, 687, 670, 654

MS (EI, 70 eV) m/z (%): 369 (100) [M^+], 312 (16).

HRMS (EI): m/z calc. for [$C_{21}H_{20}ClNOS$] 369.0954, found: 369.0952.

Preparation of 6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-4-((4-methoxybenzyl)oxy)-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (66)



To a solution of NaH (52 mg, 60w% suspension in paraffin oil, 1.0 mmol, 1.3 equiv) in anhydrous DMF (2 mL) was added (4-methoxyphenyl)methanol (166 mg, 1.2 mmol, 1.2 equiv) at 0 °C and the reaction mixture was stirred for 10 min.[207] Then, 6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-4-chloro-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (**65**; 367 mg, 1.0 mmol, 1.0 equiv) was added slowly at 0 °C and the reaction was heated under reflux for 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacou*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 10:1) afforded **66** as a yellow solid (296 mg, 63%).

mp: 198.7 – 200.2 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.50 – 7.49 (m, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.29 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.06 (dd, *J* = 4.9, 3.7 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.87 (s, 1 H), 6.78 (s, 1H), 5.20 (s, 2H), 3.83 (s, 3H), 2.12 – 1.79 (m, 15H).

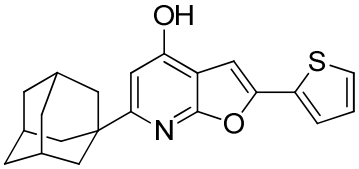
^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 166.6, 162.9, 159.8, 159.7, 148.5, 133.0, 129.6, 127.9, 127.9, 125.7, 124.8, 114.1, 108.5, 98.8, 97.7, 70.3, 55.3, 42.2, 39.4, 36.8, 28.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2902, 2846, 1608, 1597, 1517, 1454, 1348, 1339, 1305, 1263, 1193, 1182, 1174, 1094, 1080, 1053, 1041, 1031, 1000, 980, 961, 937, 856, 830, 812, 790, 772, 760, 744, 704, 692, 661

MS (EI, 70 eV) m/z (%): 471 (14) [M^+], 351 (12), 121 (100).

HRMS (EI): m/z calc. for [$C_{29}H_{29}NO_3S$] 471.1868, found: 471.1874.

Preparation of 6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2-(thiophen-2-yl)furo[2,3-*b*]pyridin-4-ol (67)



To a solution of 6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-4-((4-methoxybenzyl)oxy)-2-(thiophen-2-yl)furo[2,3-*b*]pyridine (**66**, 472 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (1.5 mL) and the reaction mixture was stirred at room temperature for 1.5 h.[208] Evaporation of the solvents *in vacuo* and purification of the crude product by flash chromatography (SiO_2, *i*-hexane/Et_2O = 4:1) afforded **67** as a colorless solid (296 mg, 63%).

mp: 214.9 – 216.6 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ (ppm): 11.08 (s, 1H), 7.62 (dd, *J* = 18.9, 4.0 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.66 (s, 1H), 2.05 – 1.73 (m, 15H).

^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ (ppm): 165.6, 162.7, 158.8, 147.0, 132.1, 128.4, 126.8, 124.8, 107.1, 101.7, 97.8, 41.6, 38.5, 36.3, 28.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2903, 2848, 1607, 1588, 1468, 1449, 1431, 1418, 1388, 1349, 1312, 1272, 1248, 1236, 1146, 1090, 1079, 1045, 996, 940, 847, 838, 815, 800, 764, 702, 692, 681.

MS (EI, 70 eV) m/z (%): 351 (100) [M^+], 294 (12).

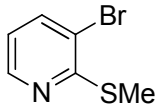
HRMS (EI): m/z calc. for [$C_{21}H_{21}NO_2S$] 351.1293, found: 351.1287.

4. NEW *IN SITU* METALATIONS OF FUNCTIONALIZED ARENES AND HETEROCYCLES WITH TMPLI IN THE PRESENCE OF $ZnCl_2$ AND OTHER METAL SALTS

4.1 PREPARATION OF STARTING MATERIALS

All reagents were obtained from commercial sources.

Preparation of 3-bromo-2-(methylthio)pyridine (68a)



To a solution of 3-bromopyridine (3.16 g, 20.0 mmol, 1.0 equiv) in anhydrous THF (60 mL) was added TMPMgCl·LiCl (1.10 M, 30.0 mmol, 1.5 equiv) at -60 °C and the reaction mixture was allowed to warm to -40 °C within 2 h. Then, neat *S*-methyl methanesulfonothioate (3.30 g, 24.0 mmol, 1.2 equiv) was added and the reaction mixture was allowed to warm to room temperature, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 80:1) afforded **68a** as a yellowish oil (3.45 g, 84%).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.38 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.85 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.53 (s, 3H).

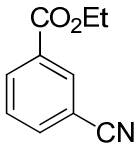
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.3, 147.5, 138.8, 119.6, 119.0, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2924, 1564, 1537, 1430, 1382, 1314, 1246, 1230, 1149, 1141, 1118, 1059, 1008, 963, 872, 781, 761, 744, 724, 701, 689, 681, 679, 677, 671, 668, 661, 658, 655, 653, 652.

MS (EI, 70 eV) m/z (%): 203 (30), 157 (14), 124 (100), 82 (16), 78 (39).

HRMS (EI): m/z calc. for [C_6H_6BrNS] 202.9404, found: 202.9395.

Preparation of ethyl 3-cyanobenzoate (73)[227]



The title compound was prepared from 3-cyanobenzoic acid (2.94 g, 20.0 mmol, 1.0 equiv) and sulfuric acid (1.84 g, 96 w%, 18.0 mmol, 0.9 equiv) in ethanol (40 mL) at 85 °C for 8 h. After cooling to room temperature, the reaction mixture was quenched

[227] Spectral data are in full accordance to those reported in the literature: I. A. Azath, P. Suresh, K. Pitchumani, *New. J. Chem.* **2012**, *36*, 2334.

with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **73** as a colorless solid (3.30 g, 94%).

mp: 54.6 – 56.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.31 (s, 1H), 8.27 – 8.24 (m, 1H), 7.83 – 7.79 (m, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 164.5, 135.8, 133.6, 133.2, 131.7, 129.3, 117.9, 112.9, 61.7, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2983, 2227, 1719, 1699, 1695, 1680, 1608, 1580, 1483, 1477, 1446, 1432, 1395, 1366, 1307, 1287, 1280, 1191, 1173, 1160, 1144, 1119, 1106, 1091, 1024, 998, 947, 934, 916, 864, 822, 781, 765, 749, 739, 683, 667.

MS (EI, 70 eV) m/z (%): 175 (22), 147 (38), 130 (100), 102 (37), 75 (12).

HRMS (EI): m/z calc. for [$C_{10}H_9NO_2$] 175.0633, found: 175.0633.

4.2 TYPICAL PROCEDURES

Typical procedure 1 (TP1): Metalation/transmetalation with $MgCl_2 \cdot 2LiCl$

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic compound (1.0 equiv) in anhydrous THF (0.2 – 0.25 M solution), $MgCl_2$ (0.5 M in THF, 1.1 equiv.) and LiCl (0.7 M in THF, 2.2 equiv) and the solution was cooled to -78 ºC. Then, TMPLi (1.5 equiv) was added drowpsie. The corresponding electrophile was added (0.9 – 1.0 equiv) afterwards and stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with H_2O, sat. aq. NH_4Cl, or $Na_2S_2O_3$ solutions and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 2 (TP2): Metalation/transmetalation with $ZnCl_2 \cdot 2LiCl$

A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic compound (1.0 equiv) in anhydrous THF (0.2 – 0.25 M solution), $ZnCl_2$ (1.0 M in THF, 1.1 equiv) and LiCl (0.7 M in THF, 2.2 equiv) and the solution was cooled to -78 ºC. Then, TMPLi (1.5 equiv) was added drowpsie. The corresponding electrophile was added (0.9 – 1.0 equiv) afterwards and stirring was

continued until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with H_2O, sat. aq. NH_4Cl, or $Na_2S_2O_3$ solutions and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 3 (TP3): Metalation/transmetalation with $LaCl_3 \cdot 2LiCl$

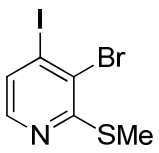
A dry and argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic compound (1.0 equiv) in anhydrous THF (0.2 – 0.25 M solution) and $LaCl_3 \cdot 2LiCl$ (1.0 M in THF, 1.1 equiv) and the solution was cooled to -78 ºC. Then, TMPLi (1.5 equiv) was added drowpsie. The corresponding electrophile was added (0.9 equiv) afterwards and stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with H_2O, sat. aq. NH_4Cl, or $Na_2S_2O_3$ solutions and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

Typical procedure 3 (TP3): *Negishi* cross-coupling reactions

To the freshly prepared zinc reagent, $Pd(dba)_2$ (2 mol%), $P(2\text{-furyl})_3$ (4 mol%) and the aryl iodide (0.7 – 1.0 equiv) were added at -78 °C and the reaction mixture was allowed to warm to room temperature. Stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots). The reaction mixture was then quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a sat. aq. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

4.3 METALATION OF SENSITIVE FUNCTIONALIZED HETEROARENES USING TMPLI IN THE PRESENCE OF METAL SALTS

Preparation of 3-bromo-4-iodo-2-(methylthio)pyridine (71a)



Prepared using three different methods.

Method A: Prepared according to **TP2** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M,

1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, a solution of I_2 (381 mg, 1.5 mmol, 1.5 equiv) in anhydrous THF (1.5 mL) was added and the reaction mixture was stirred at -78 °C for 5 min and 1 h at room temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 200:1) afforded **71a** as colorless solid (249 mg, 76%).

Method B: Prepared according to **TP1** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $MgCl_2$ (0.5 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, a solution of I_2 (381 mg, 1.5 mmol, 1.5 equiv) in anhydrous THF (1.5 mL) was added and the reaction mixture was stirred at -78 °C for 5 min and 1 h at room temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 200:1) afforded **71a** as colorless solid (288 mg, 87%).

Method C: Prepared according to **TP3** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $LaCl_3 \cdot 2LiCl$ (0.5 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, a solution of I_2 (381 mg, 1.5 mmol, 1.5 equiv) in anhydrous THF (1.5 mL) was added and the reaction mixture was stirred at -78 °C for 5 min and 1 h at room temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 200:1) afforded **71a** as colorless solid (224 mg, 68%).

mp: 119.0 – 121.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.97 (d, *J* = 5.1 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 2.48 (s, 3H).

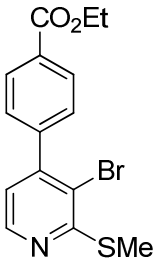
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.7, 146.9, 129.9, 126.0, 112.7, 15.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2920, 1530, 1507, 1484, 1418, 1416, 1322, 1315, 1267, 1257, 1204, 1192, 1146, 1103, 1005, 964, 818, 761, 729, 722, 695, 679, 668, 663, 661, 656, 653.

MS (EI, 70 eV) m/z (%): 329 (12), 250 (49), 167 (27), 149 (94), 83 (29), 71 (49), 70 (31), 69 (39), 57 (89), 56 (28), 55 (43), 44 (84), 43 (100).

HRMS (EI): m/z calc. for [C_6H_5BrINS] 328.8371, found: 328.8364.

Preparation of ethyl 4-[3-bromo-2-(methylthio)pyridin-4-yl]benzoate (71b)



Prepared according to **TP2** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. According to **TP3** the corresponding zinc reagent was reacted with ethyl 4-iodobenzoate (**72a**; 248 mg, 0.9 mmol, 0.9 equiv) at that temperature for 5 min and was allowed to warm to room temperature within 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **71b** as an off-white solid (252 mg, 80%).

mp: 75.0 – 76.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.41 (d, J = 4.9 Hz, 1H), 8.12 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 4.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.57 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H).

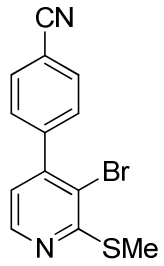
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.0, 161.0, 149.0, 147.2, 143.1, 130.6, 129.5, 128.8, 120.5, 118.6, 61.2, 15.0, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 1707, 1684, 1568, 1516, 1465, 1438, 1404, 1362, 1333, 1308, 1299, 1273, 1218, 1202, 1176, 1161, 1122, 1116, 1105, 1100, 1062, 1026, 1019, 1010, 995, 983, 962, 873, 868, 855, 845, 839, 820, 801, 772, 758, 749, 704, 686, 668.

MS (EI, 70 eV) m/z (%): 353 (61), 352 (16), 351 (67), 272 (55), 244 (55), 200 (21), 199 (100), 198 (29), 154 (18), 153 (23), 152 (19), 126 (17).

HRMS (EI): m/z calc. for [$C_{15}H_{14}BrNO_2S$] 350.9929, found: 350.9926.

Preparation of 4-(3-bromo-2-(methylthio)pyridin-4-yl)benzonitrile (71c)



Prepared according to **TP2** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. According to **TP3** the corresponding zinc reagent was reacted with 4-iodobenzonitrile (206 mg, 0.9 mmol, 0.9 equiv) at that temperature for 5 min and was allowed to warm to room temperature within 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **71c** as a yellowish solid (169 mg, 62%).

mp: 152.1 – 154.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.43 (d, *J* = 4.9 Hz, 1H), 7.74 (d, *J* = 8.2Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 4.9 Hz, 1H), 2.57 (s, 3H).

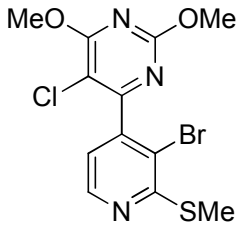
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 161.4, 147.9, 147.4, 143.3, 132.1, 129.6, 120.2, 118.3, 118.3, 112.6, 15.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2918, 2229, 1566, 1510, 1503, 1436, 1401, 1332, 1309, 1295, 1202, 1180, 1120, 1112, 1061, 1022, 1010, 1002, 976, 961, 955, 850, 820, 802, 771, 762, 748, 728, 723, 708, 685, 680.

MS (EI, 70 eV) m/z (%): 304 (27),225 (100), 179 (29), 152 (22).

HRMS (EI): m/z calc. for [$C_{13}H_9BrN_2S$] 303.9670, found: 303.9660.

Preparation of 4-(3-bromo-2-(methylthio)pyridin-4-yl)-5-chloro-2,6-dimethoxy-pyrimidine (71d)



Prepared according to **TP2** from 3-bromo-2-(methylthio)pyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. According to **TP3** the corresponding zinc reagent was reacted with 5-chloro-4-iodo-2,6-dimethoxypyrimidine (**72c**; 270 mg, 0.9 mmol, 0.9 equiv) at that temperature for 5 min, was then allowed to warm to room temperature and heated at 50 °C for 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **71d** as a yellowish solid (130 mg, 39%).

mp: 163.7 – 165.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.47 (d, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 4.9 Hz, 1H), 4.10 (s, 3H), 3.97 (s, 3H), 2.57 (s, 3H).

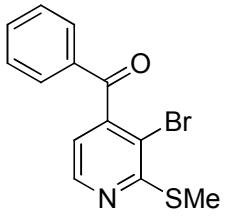
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.9, 162.6, 162.5, 160.9, 147.4, 145.0, 119.1, 118.0, 109.0, 55.5, 55.3, 14.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2955, 2926, 1553, 1517, 1487, 1460, 1441, 1387, 1364, 1346, 1336, 1254, 1230, 1219, 1194, 1172, 1119, 1108, 1046, 1032, 1012, 948, 899, 847, 790, 765, 759, 696, 683, 664.

MS (EI, 70 eV) m/z (%): 375 (64), 298 (39), 297 (21), 296 (100), 261 (99).

HRMS (EI): m/z calc. for [$C_{12}H_{11}BrClN_3O_2S$] 374.9444, found: 374.9436.

Preparation of (3-bromo-2-(methylthio)pyridin-4-yl)(phenyl)methanone (71e)



Prepared using three different methods.

Method A: Prepared according to **TP2** from 3-bromopyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, CuCN·2LiCl (1.0 M, 1.5 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 15 min at -78 °C. Then, benzoyl chloride (**72d**; 127 mg, 0.9 mmol, 0.9 equiv) was added and the reaction mixture was allowed to warm room temperature within 16 h. The reaction mixture was quenched with a conc. aq. NH_4Cl/NH_3 (2:1) solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **71e** as a yellowish solid (60 mg, 22%).

Method B: Prepared according to **TP3** from 3-bromopyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $LaCl_3$·2LiCl (0.5 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, benzoyl chloride (**72d**; 127 mg, 0.9 mmol, 0.9 equiv) was added and the reaction mixture was allowed to warm room temperature within 16 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **71e** as a yellowish solid (82 mg, 30%).

Method C: Prepared according to **TP2** from 3-bromopyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 2 mol%) and benzoyl chloride (**72d**; 127 mg, 0.9 mmol, 0.9 equiv) were added. The reaction mixture was stirred at that temperature for 5 min and allowed to warm to room temperature within 16 h. Then it was heated to 50 °C for 4 h, quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and

concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **71e** as a yellowish solid (154 mg, 56%).

mp: 94.7 – 97.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 4.8 Hz, 1H), 2.59 (s, 3H).

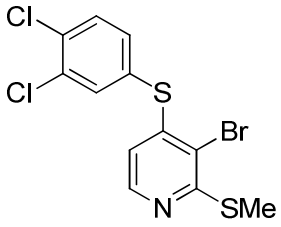
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 193.6, 161.2, 147.9, 147.5, 134.7, 134.4, 130.1, 128.9, 117.4, 115.1, 14.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2924, 2920, 2852, 1720, 1670, 1651, 1592, 1582, 1566, 1556, 1514, 1489, 1448, 1435, 1425, 1408, 1332, 1317, 1279, 1225, 1202, 1180, 1171, 1158, 1144, 1109, 1105, 1085, 1070, 1054, 1017, 1000, 977, 970, 957, 937, 919, 902, 889, 881, 872, 869, 847, 839, 828, 821, 804, 772, 749, 743, 734, 709, 703, 687, 682, 657.

MS (EI, 70 eV) m/z (%): 309 (66), 307 (64), 294 (64), 293 (45), 247 (34), 228 (96), 199 (22), 185 (41), 183 (55), 105 (82), 77 (100).

HRMS (EI): m/z calc. for [$C_{13}H_{10}BrNOS$] 306.9666, found: 306.9662.

Preparation of 3-bromo-4-((3,4-dichlorophenyl)thio)-2-(methylthio)pyridine (71f)



Prepared according to **TP1** from 3-bromopyridine (**68a**; 204 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $MgCl_2$ (0.5 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, *S*-(3,4-dichlorophenyl) benzenesulfonothioate[197] (**72e**; 287 mg, 0.9 mmol, 0.9 equiv) dissolved in THF (1 mL) was added and the reactions mixture was stirred at -78 °C for 5 min and 6 h at room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 80:1) afforded **71f** as a colorless solid (205 mg, 60%).

mp: 146.8 – 148.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.10 (d, *J* = 5.3 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.22 (d, *J* = 5.3 Hz, 1H), 2.53 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 160.1, 149.8, 146.7, 137.0, 135.0, 134.7, 134.1, 131.8, 129.5, 116.3, 115.8, 14.8.

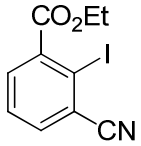
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2361, 2358, 2357, 1546, 1511, 1506, 1452, 1440, 1418, 1364, 1335, 1312, 1305, 1245, 1200, 1158, 1145, 1138, 1131, 1129, 1122, 1109, 1097, 1034, 1014, 1007, 986, 963, 952, 878, 820, 814, 810, 786, 759, 725, 714, 697, 675, 668, 662.

MS (EI, 70 eV) m/z (%): 383 (38), 382 (16), 381 (74), 380 (15), 379 (41), 304 (17), 301 (18), 300 (100), 142 (16).

HRMS (EI): m/z calc. for [$C_{12}H_8BrCl_2NS_2$] 378.8659, found: 378.8651.

4.4 UNPRECEDENTED REGIOSELECTIVITIES IN THE METALATION OF (HETERO)ARENES USING TMPLI IN THE PRESENCE OF METAL SALTS

Preparation of ethyl 3-cyano-2-iodobenzoate (74)



To a solution of ethyl 3-cyanobenzoate (**73**; 175 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) was added TMPMgCl·LiCl (1.10 M, 1.1 mmol, 1.1 equiv) at room temperature and the reaction mixture was stirred for 1 h. Then, a solution of I_2 (254 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) was added and the reaction mixture was stirred at that temperature for 1 h. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **74** as a colorless solid (137 mg, 46%).

mp: 73.0 – 74.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.8, 138.7, 136.2, 133.5, 128.4, 123.7, 119.4, 98.0, 62.4, 14.1.

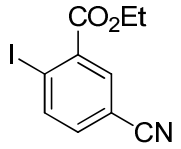
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2231, 1722, 1699, 1695, 1682, 1572, 1477, 1448, 1443, 1410, 1394, 1365, 1280, 1249, 1231, 1185, 1166, 1142, 1116, 1065, 1021, 995, 970, 963, 956, 952, 943, 932, 919, 899, 895, 888, 884, 869, 851, 846, 841, 835, 826, 791,

787, 777, 753, 714, 707, 703, 699, 692, 683, 680, 677, 675, 674, 669, 667, 661, 659, 656, 653.

MS (EI, 70 eV) m/z (%): 301 (61), 273 (35), 256 (100), 228 (26), 101 (32), 75 (19).

HRMS (EI): m/z calc. for [$C_{10}H_8INO_2$] 300.9600, found: 300.9598.

Preparation of ethyl 5-cyano-2-iodobenzoate (75a)



Prepared according to **TP2** from ethyl 3-cyanobenzoate (**73**; 104 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, a solution of I_2 (254 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) was added and the reaction mixture was stirred at -78 °C for 10 min and 1 h at room temperature. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 20:1) afforded **75a** as a colorless solid (164 mg, 54%).

mp: 98.5 – 100.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.13 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.42 (q, *J* = 7.1Hz, 2 H), 1.42 (t, *J* = 7.1Hz, 3 H).

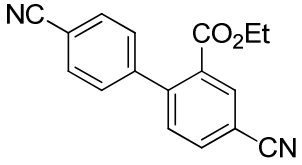
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 164.6, 142.5, 136.5, 134.5, 133.9, 117.3, 112.3, 100.2, 62.5, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2231, 1736, 1586, 1461, 1456, 1395, 1368, 1295, 1277, 1244, 1192, 1154, 1153, 1118, 1110, 1099, 1023, 1018, 969, 911, 867, 832, 777.

MS (EI, 70 eV) m/z (%): 301 (82), 273 (48), 256 (100), 228 (31), 178 (19), 127 (24), 101 (22), 71 (20).

HRMS (EI): m/z calc. for [$C_{10}H_8INO_2$] 300.9600, found: 300.9587.

Preparation of ethyl 4,4'-dicyano-[1,1'-biphenyl]-2-carboxylate (75b)



Prepared according to **TP2** from ethyl 3-cyanobenzoate (**73**; 104 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. According to **TP3** the corresponding zinc reagent was reacted with 4-iodo-benzonitrile (**72b**; 160 mg, 0.7 mmol, 0.7 equiv) at that temperature for 5 min and 4 h at room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **75b** as an off-white solid (163 mg, 84%).

mp: 123.8 – 125.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.22 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 1.09 (t, *J* = 7.1 Hz, 3 H).

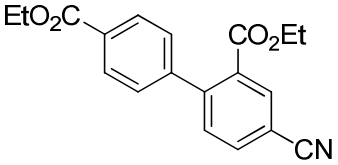
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.4, 145.1, 144.4, 134.5, 134.1, 131.9, 131.7, 131.4, 128.9, 118.3, 117.4, 112.6, 112.1, 61.9, 13.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2922, 2229, 2224, 1724, 1684, 1675, 1603, 1587, 1495, 1482, 1473, 1464, 1454, 1412, 1400, 1387, 1364, 1313, 1294, 1282, 1245, 1188, 1157, 1141, 1128, 1116, 1100, 1015, 1006, 990, 971, 964, 948, 919, 884, 867, 860, 852, 830, 791, 755, 748, 731, 729, 727, 724, 721, 717, 701, 694, 684, 682, 679, 676, 668, 661, 655, 653.

MS (EI, 70 eV) m/z (%): 276 (31), 248 (28), 232 (18), 231 (100), 203 (20), 202 (16), 176 (25).

HRMS (EI): m/z calc. for [$C_{17}H_{12}N_2O_2$] 276.0899, found: 276.0892.

Preparation of diethyl 4-cyano-[1,1'-biphenyl]-2,4'-dicarboxylate (75c)



Prepared according to **TP2** from ethyl 3-cyanobenzoate (**73**; 104 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. According to **TP3** the corresponding zinc reagent was reacted with ethyl 4-iodobenzoate (**72a**; 193 mg, 0.7 mmol, 0.7 equiv) at that temperature for 5 min and 4 h at room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in*

vacuo. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 6:1) afforded **75c** as a colorless solid (196 mg, 87%).

mp: 62.8 – 64.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.16 (d, *J* = 1.4 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

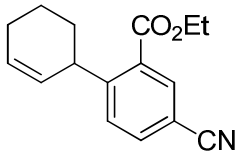
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.1, 145.9, 144.1, 134.2, 133.8, 132.1, 131.4, 130.2, 129.4, 128.1, 117.6, 112.0, 61.8, 61.1, 14.3, 13.7. (One signal not observed; possible coincidental isochronicity.)

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2987, 2233, 1710, 1697, 1671, 1659, 1652, 1611, 1602, 1485, 1476, 1464, 1453, 1443, 1407, 1387, 1366, 1361, 1310, 1289, 1273, 1253, 1190, 1180, 1170, 1149, 1112, 1106, 1101, 1091, 1023, 1017, 1004, 971, 948, 924, 868, 848, 798, 793, 777, 761, 729, 712, 683, 679, 677, 672, 668, 663, 661, 658, 656, 655, 653.

MS (EI, 70 eV) m/z (%): 323 (44), 279(18), 278 (100), 250 (27), 206 (30), 177 (20).

HRMS (EI): m/z calc. for [$C_{19}H_{17}NO_4$] 323.1158, found: 323.1151.

Preparation of ethyl 4-cyano-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-carboxylate (75d)



Prepared according to **TP2** from ethyl 3-cyanobenzoate (**73**; 104 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, CuCN·2LiCl (1.0 M, 1.5 mmol, 1.5 equiv) was added and the reaction mixture was stirred at -78 °C for 15 min. Then, 3-bromocyclohex-1-ene (**72g**; 113 mg, 0.7 mmol, 0.7 equiv) was added and the reaction mixture was allowed to warm to -40 °C within 4 h. The reaction mixture was quenched with a conc. aq. NH_4Cl/NH_3 (2:1) solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **75d** as a colorless solid (140 mg, 79%).

mp: 53.5 – 55.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09 (d, *J* = 1.7 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 6.00 - 5.93 (m, 1H), 5.58 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.41 - 4.28 (m, 3H), 2.19 - 2.03 (m, 3H), 1.75 - 1.58 (m, 2H), 1.48 - 1.36 (m, 4H).

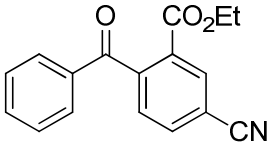
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.0, 153.0, 134.4, 134.0, 131.1, 130.1, 129.7, 128.8, 118.2, 109.9, 61.6, 38.1, 32.0, 24.8, 21.0, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2978, 2925, 2918, 2854, 2837, 2231, 1723, 1695, 1684, 1674, 1603, 1557, 1486, 1476, 1467, 1455, 1440, 1392, 1388, 1365, 1313, 1294, 1278, 1270, 1240, 1221, 1192, 1184, 1148, 1135, 1122, 1112, 1081, 1073, 1044, 1024, 981, 941, 924, 915, 901, 881, 870, 846, 824, 818, 804, 788, 768, 750, 748, 742, 731, 723, 716, 707, 697, 696, 691, 682, 668, 664, 658.

MS (EI, 70 eV) m/z (%): 255 (20), 210 (23), 209 (100), 208 (45), 191 (38), 190 (45), 180 (23), 153 (24), 149 (37), 140 (21).

HRMS (EI): m/z calc. for [$C_{16}H_{17}NO_2$] 255.1259, found: 255.1261.

Preparation of ethyl 2-benzoyl-5-cyanobenzoate (75e)



Prepared according to **TP2** from ethyl 3-cyanobenzoate (**73**; 104 mg, 1.0 mmol, 1.0 equiv), TMPLi (0.66 M, 1.5 mmol, 1.5 equiv), $ZnCl_2$ (1.0 M, 1.1 mmol, 1.1 equiv) and LiCl (0.7 M, 2.2 mmol, 2.2 equiv) in anhydrous THF (2 mL) at -78 °C. After the addition of TMPLi, CuCN·2LiCl (1.0 M, 1.5 mmol, 1.5 equiv) was added and the reaction mixture was stirred at -78 °C for 15 minutes. Then, benzoyl chloride (**72d**; 98 mg, 0.7 mmol, 0.7 equiv) was added and the reaction mixture was allowed to warm room temperature overnight. The reaction mixture was quenched with a conc. aq. NH_4Cl/NH_3 (2:1) solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2, *i*-hexane/EtOAc = 10:1) afforded **75e** as a colorless solid (97 mg, 50%).

mp: 96.2 – 98.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.36 (d, *J* = 1.3 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.72 – 7.69 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.42 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 195.0, 163.8, 145.5, 136.1, 135.4, 133.9, 133.8, 130.4, 129.3, 128.7, 128.5, 117.2, 113.8, 62.3, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2962, 2958, 2937, 2925, 2234, 1721, 1694, 1666, 1608, 1596, 1582, 1472, 1451, 1409, 1391, 1361, 1318, 1295, 1272, 1256, 1190, 1164, 1146, 1126, 1115, 1088, 1071, 1028, 1011, 999, 987, 943, 931, 911, 861, 844, 805, 797, 777, 732, 713, 692, 685, 673, 667.

MS (EI, 70 eV) m/z (%): 279 (26), 234 (32), 202 (19), 174 (54), 105 (100), 77 (33).

HRMS (EI): m/z calc. for [$C_{17}H_{13}NO_3$] 279.0895, found: 279.0896.

D. APPENDIX

1. LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
Cbz	carboxybenzyl
conc.	concentrated
d	doublet (NMR) / day
dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzo-1,4-quinone
DIPEA	*N*,*N*-di*iso*propylethylamine
DMA	*N*,*N*-dimethylacetamide
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMG	directed metalation group
DMPU	*N*,*N*'-dimethylpropyleneurea
D*o*M	directed *ortho*-metalation
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMSO	dimethyl sulfoxide
equiv	equivalent
E^+	electrophile
EI	electron ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hal	halogen

Hex	hexyl
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	Hertz
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
L	ligand
LDA	lithium *N*,*N*-di*iso*propylamide
M	mol/L
m	*meta*
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute
MEM	methoxyethoxymethyl
MOM	methoxymethyl
mp	melting point
MWI	microwave irradiation
MS	mass spectroscopy
MHz	Megahertz
*n*Bu	*n*-butyl
*n*Pr	*n*-propyl
NBS	*N*-bromosuccinimide
NEP	*N*-ethyl-2-pyrrolidone
NFSI	*N*-fluorobenzenesulfinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidin-2-one
o	*ortho*
p	*para*
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PG	protective group
Ph	phenyl

Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
py	pyridine
R	organic substituent
rpm	revolutions per minute
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
T	temperature
t	reaction time
TBDMS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethane-1,2-diamine
TMP	2,2,6,6-tetramethylpiperidyl
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl / tosylate
TP	typical procedure

2. X-RAY DATA FOR COMPOUNDS **18**, **23A**, **23B**, **27A**, **27B** AND **37**

Compound 18

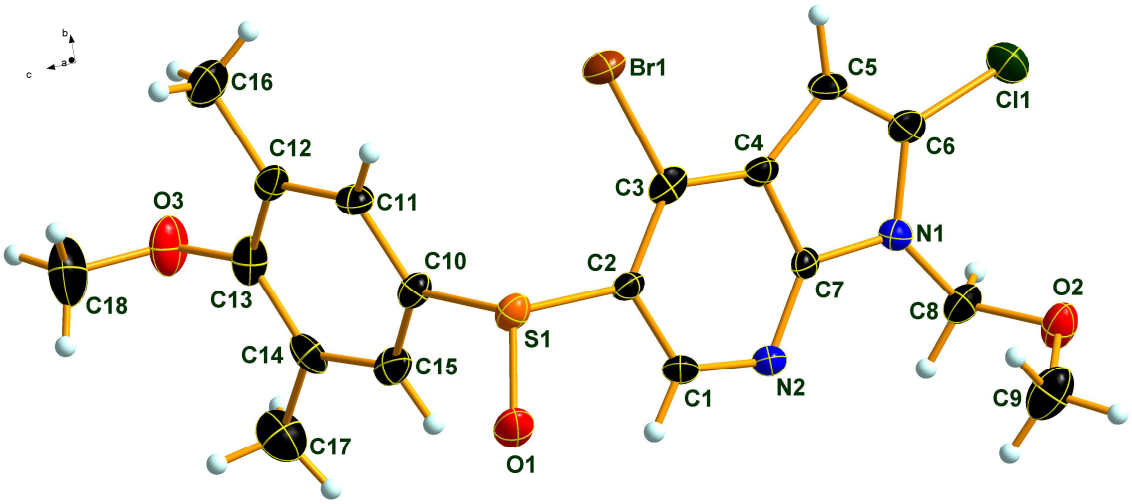


Figure 5: DIAMOND view of the molecular structure of compound **18** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 12: Molecular structure of compound **18** in the crystal; selected atom distances (in Å).

Br1 – C3	1.888(4)	C1 – C2	1.393(6)
Cl1 – C6	1.704(5)	C2 – C3	1.388(6)
S1 – O1	1.497(3)	C3 – C4	1.399(7)
S1 – C2	1.812(4)	C4 – C5	1.423(6)
S1 – C10	1.789(5)	C4 – C7	1.412(7)
O2 – C8	1.402(6)	C5 – C6	1.357(7)
O2 – C9	1.434(7)	C10 – C11	1.394(7)
O3 – C13	1.382(6)	C10 – C15	1.386(7)
O3 – C18	1.428(6)	C11 – C12	1.402(7)
N1 – C6	1.397(7)	C12 – C13	1.393(7)
N1 – C7	1.383(5)	C12 – C16	1.511(7)
N1 – C8	1.455(7)	C13 – C14	1.411(7)
N2 – C1	1.337(6)	C14 – C15	1.391(7)
N2 – C7	1.335(6)	C14 – C17	1.501(7)

Table 13: Molecular structure of compound **18** in the crystal; selected bond angles (in °).

O1 – S1 – C2	105.7(2)	Cl1 – C6 – C5	128.6(4)
O1 – S1 – C10	106.2(2)	N1 – C6 – C5	111.6(4)
C2 – S1 – C10	98.8(2)	N1 – C7 – N2	124.4(4)
C8 – O2 – C9	112.8(4)	N1 – C7 – C4	108.2(4)
C13 – O3 – C18	113.5(4)	N2 – C7 – C4	127.4(4)
C6 – N1 – C7	106.5(4)	O2 – C8 – N1	113.8(4)
C6 – N1 – C8	127.1(4)	S1 – C10 – C11	117.7(4)
C7 – N1 – C8	126.3(4)	S1 – C10 – C15	120.9(4)
C1 – N2 – C7	114.0(4)	C11 – C10 – C15	121.2(4)
N2 – C1 – C2	124.5(4)	C10 – C11 – C12	119.9(4)
S1 – C2 – C1	119.1(3)	C11 – C12 – C13	118.0(4)
S1 – C2 – C3	120.8(3)	C11 – C12 – C16	119.8(4)
C1 – C2 – C3	120.0(4)	C13 – C12 – C16	122.2(4)
Br1 – C3 – C2	123.4(3)	O3 – C13 – C12	119.3(4)
Br1 – C3 – C4	118.7(3)	O3 – C13 – C14	118.1(4)
C2 – C3 – C4	117.9(4)	C12 – C13 – C14	122.6(4)
C3 – C4 – C5	136.1(4)	C13 – C14 – C15	117.8(5)
C3 – C4 – C7	116.1(4)	C13 – C14 – C17	120.8(4)
C5 – C4 – C7	107.8(4)	C15 – C14 – C17	121.4(5)
C4 – C5 – C6	106.0(4)	C10 – C15 – C14	120.4(5)
Cl1 – C6 – N1	119.8(4)		

Table 14: Molecular structure of compound **18** in the crystal; selected torsion angles (in °).

O1 – S1 – C10 – C11	143.8(4)	C1 – C2 – C3 – Br1	-179.1(3)
C2 – S1 – C10 – C11	-106.9(4)	Br1 – C3 – C4 – C7	179.9(3)
O1 – S1 – C10 – C15	-30.8(4)	C2 – C3 – C4 – C5	-178.0(5)
O1 – S1 – C2 – C1	14.0(4)	C2 – C3 – C4 – C7	0.2(6)
C10 – S1 – C2 – C1	-95.7(4)	Br1 – C3 – C4 – C5	1.7(8)
O1 – S1 – C2 – C3	-161.7(4)	C3 – C4 – C5 – C6	179.6(6)
C10 – S1 – C2 – C3	88.6(4)	C5 – C4 – C7 – N2	178.0(4)
C2 – S1 – C10 – C15	78.4(4)	C3 – C4 – C7 – N1	-180.0(4)
C9 – O2 – C8 – N1	71.5(5)	C3 – C4 – C7 – N2	-0.7(7)

C18 – O3 – C13 – C12	-82.8(6)	C7 – C4 – C5 – C6	1.4(5)
C18 – O3 – C13 – C14	98.3(5)	C5 – C4 – C7 – N1	-1.3(5)
C6 – N1 – C8 – O2	75.1(6)	C4 – C5 – C6 – Cl1	175.9(4)
C7 – N1 – C8 – O2	-108.4(5)	C4 – C5 – C6 – N1	-0.9(6)
C8 – N1 – C6 – Cl1	0.1(7)	S1 – C10 – C11 – C12	-174.8(4)
C8 – N1 – C6 – C5	177.2(4)	C15 – C10 – C11 – C12	-0.2(7)
C7 – N1 – C6 – Cl1	-177.0(3)	S1 – C10 – C15 – C14	172.8(4)
C6 – N1 – C7 – N2	-178.6(4)	C11 – C10 – C15 – C14	-1.7(7)
C6 – N1 – C7 – C4	0.8(5)	C10 – C11 – C12 – C13	1.2(7)
C7 – N1 – C6 – C5	0.1(5)	C10 – C11 – C12 – C16	-179.9(5)
C8 – N1 – C7 – C4	-176.4(4)	C11 – C12 – C13 – O3	-179.3(4)
C8 – N1 – C7 – N2	4.3(7)	C11 – C12 – C13 – C14	-0.4(7)
C1 – N2 – C7 – C4	0.4(7)	C16 – C12 – C13 – O3	1.7(7)
C1 – N2 – C7 – N1	179.5(4)	C16 – C12 – C13 – C14	-179.3(5)
C7 – N2 – C1 – C2	0.5(6)	O3 – C13 – C14 – C15	177.6(4)
N2 – C1 – C2 – C3	-0.9(7)	O3 – C13 – C14 – C17	-2.2(7)
N2 – C1 – C2 – S1	-176.7(4)	C12 – C13 – C14 – C15	-1.4(7)
S1 – C2 – C3 – Br1	-3.5(5)	C12 – C13 – C14 – C17	178.9(5)
C1 – C2 – C3 – C4	0.5(6)	C13 – C14 – C15 – C10	2.4(7)
S1 – C2 – C3 – C4	176.2(3)	C17 – C14 – C15 – C10	-177.9(5)

Compound 23a

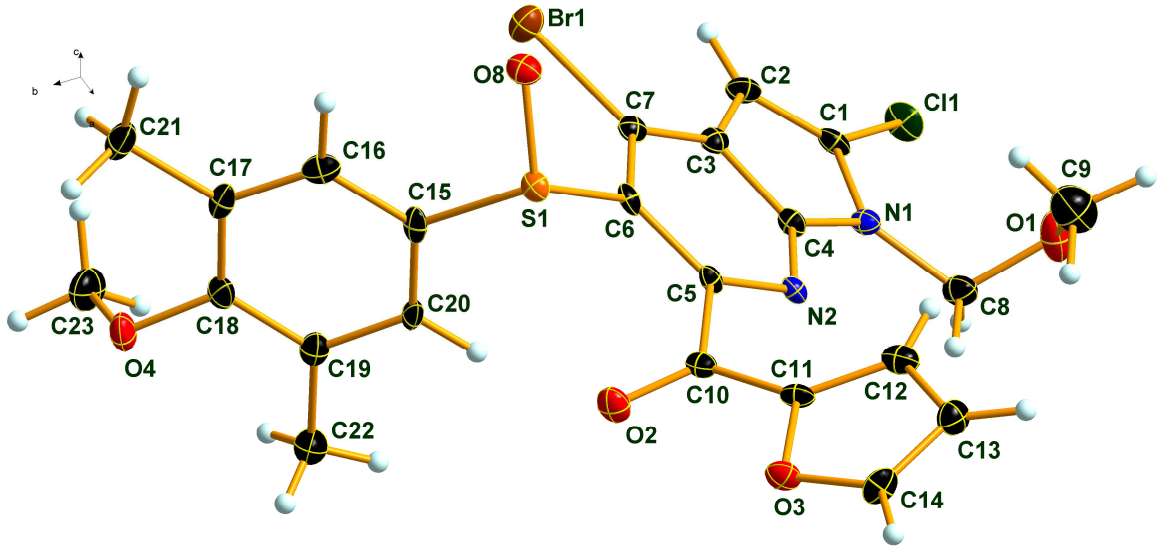


Figure 6: DIAMOND view of the molecular structure of compound **23a** (molecule A) in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 15: Molecular structure of compound **23a** (molecule A) in the crystal; selected atom distances (in Å).

Br1 – C7	1.886(3)	C2 – C3	1.419(5)
Cl1 – C1	1.706(4)	C3 – C7	1.396(5)
S1 – O8	1.499(3)	C3 – C4	1.427(5)
S1 – C15	1.795(4)	C5 – C6	1.426(5)
S1 – C6	1.823(4)	C5 – C10	1.522(5)
O1 – C8	1.388(6)	C6 – C7	1.395(5)
O1 – C9	1.402(6)	C10 – C11	1.455(5)
O2 – C10	1.213(4)	C11 – C12	1.361(6)
O3 – C14	1.374(5)	C12 – C13	1.407(6)
O3 – C11	1.381(4)	C13 – C14	1.348(6)
O4 – C18	1.388(4)	C15 – C16	1.393(6)
O4 – C23	1.431(6)	C15 – C20	1.393(5)
N1 – C1	1.384(5)	C16 – C17	1.397(7)
N1 – C8	1.457(6)	C17 – C18	1.405(5)
N1 – C4	1.394(4)	C17 – C21	1.505(6)
N2 – C4	1.331(4)	C18 – C19	1.401(5)
N2 – C5	1.350(4)	C19 – C22	1.504(6)

C1 – C2	1.367(5)	C19 – C20	1.403(5)

Table 16: Molecular structure of compound **23a** (molecule A) in the crystal; selected bond angles (in °).

O8 – S1 – C6	108.6(2)	Br1 – C7 – C3	118.0(2)
O8 – S1 – C15	106.9(2)	C3 – C7 – C6	118.7(3)
C6 – S1 – C15	98.4(2)	O1 – C8 – N1	113.1(4)
C8 – O1 – C9	113.4(4)	O2 – C10 – C5	118.7(3)
C11 – O3 – C14	106.0(3)	O2 – C10 – C11	122.8(3)
C18 – O4 – C23	114.9(3)	C5 – C10 – C11	118.5(3)
C4 – N1 – C8	126.4(3)	O3 – C11 – C10	115.4(3)
C1 – N1 – C8	126.9(3)	O3 – C11 – C12	109.1(3)
C1 – N1 – C4	106.7(3)	C10 – C11 – C12	135.4(4)
C4 – N2 – C5	113.9(3)	C11 – C12 – C13	107.7(4)
N1 – C1 – C2	112.2(3)	C12 – C13 – C14	106.3(4)
Cl1 – C1 – C2	128.1(3)	O3 – C14 – C13	110.8(4)
Cl1 – C1 – N1	119.7(3)	S1 – C15 – C20	121.5(3)
C1 – C2 – C3	105.7(3)	S1 – C15 – C16	117.5(3)
C2 – C3 – C4	108.0(3)	C16 – C15 – C20	120.6(3)
C2 – C3 – C7	136.1(3)	C15 – C16 – C17	121.2(4)
C4 – C3 – C7	116.0(3)	C16 – C17 – C21	121.2(4)
N1 – C4 – C3	107.4(3)	C16 – C17 – C18	117.2(4)
N2 – C4 – C3	128.0(3)	C18 – C17 – C21	121.6(4)
N1 – C4 – N2	124.5(3)	O4 – C18 – C17	118.8(3)
C6 – C5 – C10	119.9(3)	O4 – C18 – C19	118.3(3)
N2 – C5 – C6	124.2(3)	C17 – C18 – C19	122.8(3)
N2 – C5 – C10	115.7(3)	C18 – C19 – C22	121.5(3)
C5 – C6 – C7	119.1(3)	C20 – C19 – C22	120.3(3)
S1 – C6 – C5	116.9(2)	C18 – C19 – C20	118.3(3)
S1 – C6 – C7	123.7(3)	C15 – C20 – C19	119.9(3)
Br1 – C7 – C6	123.2(3)		

Table 17: Molecular structure of compound **23a** (molecule A) in the crystal; selected torsion angles (in °).

C15 – S1 – C6 – C5	-115.7(3)	C7 – C3 – C4 – N2	1.2(6)
O8 – S1 – C6 – C7	-40.4(3)	C10 – C5 – C6 – C7	-171.9(3)
O8 – S1 – C6 – C5	133.2(3)	C6 – C5 – C10 – O2	40.6(5)
C6 – S1 – C15 – C20	46.4(3)	C6 – C5 – C10 – C11	-138.8(4)
O8 – S1 – C15 – C20	158.9(3)	N2 – C5 – C6 – S1	-171.3(3)
C15 – S1 – C6 – C7	70.7(3)	N2 – C5 – C6 – C7	2.6(5)
C6 – S1 – C15 – C16	-140.8(3)	N2 – C5 – C10 – C11	46.3(5)
O8 – S1 – C15 – C16	-28.4(3)	C10 – C5 – C6 – S1	14.2(4)
C9 – O1 – C8 – N1	72.8(5)	N2 – C5 – C10 – O2	-134.4(4)
C14 – O3 – C11 – C10	-175.1(3)	S1 – C6 – C7 – C3	174.1(3)
C14 – O3 – C11 – C12	0.9(4)	S1 – C6 – C7 – Br1	-9.4(5)
C11 – O3 – C14 – C13	-0.9(4)	C5 – C6 – C7 – C3	0.6(5)
C23 – O4 – C18 – C17	90.5(4)	C5 – C6 – C7 – Br1	177.1(3)
C23 – O4 – C18 – C19	-93.0(4)	O2 – C10 – C11 – O3	1.5(5)
C8 – N1 – C4 – N2	-2.9(6)	C5 – C10 – C11 – O3	-179.2(3)
C8 – N1 – C1 – Cl1	3.5(5)	C5 – C10 – C11 – C12	6.3(6)
C4 – N1 – C1 – Cl1	-177.8(3)	O2 – C10 – C11 – C12	-173.0(4)
C1 – N1 – C8 – O1	70.6(5)	O3 – C11 – C12 – C13	-0.5(4)
C4 – N1 – C8 – O1	-107.9(5)	C10 – C11 – C12 – C13	174.2(4)
C8 – N1 – C4 – C3	178.7(4)	C11 – C12 – C13 – C14	-0.1(4)
C1 – N1 – C4 – N2	178.4(3)	C12 – C13 – C14 – O3	0.6(4)
C1 – N1 – C4 – C3	0.0(4)	S1 – C15 – C16 – C17	-172.7(3)
C4 – N1 – C1 – C2	0.5(4)	C20 – C15 – C16 – C17	0.1(5)
C8 – N1 – C1 – C2	-178.2(4)	S1 – C15 – C20 – C19	172.6(3)
C4 – N2 – C5 – C10	171.1(3)	C16 – C15 – C20 – C19	0.1(5)
C5 – N2 – C4 – N1	-176.4(3)	C15 – C16 – C17 – C21	179.3(4)
N1 – C1 – C2 – C3	-0.7(4)	C15 – C16 – C17 – C18	0.5(5)
Cl1 – C1 – C2 – C3	177.4(3)	C16 – C17 – C18 – O4	175.0(3)
C1 – C2 – C3 – C4	0.7(4)	C16 – C17 – C18 – C19	-1.5(5)
C1 – C2 – C3 – C7	-179.4(4)	C21 – C17 – C18 – O4	-3.8(5)
C2 – C3 – C7 – Br1	1.1(6)	C21 – C17 – C18 – C19	179.7(4)
C7 – C3 – C4 – N1	179.6(3)	O4 – C18 – C19 – C22	4.1(5)

C2 – C3 – C4 – N2	-178.8(4)	C17 – C18 – C19 – C20	1.7(5)
C4 – C3 – C7 – C6	-2.3(5)	C17 – C18 – C19 – C22	-179.4(4)
C2 – C3 – C7 – C6	177.7(4)	O4 – C18 – C19 – C20	-174.7(3)
C4 – C3 – C7 – Br1	-179.0(3)	C22 – C19 – C20 – C15	-179.9(3)
C2 – C3 – C4 – N1	-0.4(4)	C18 – C19 – C20 – C15	-1.0(5)

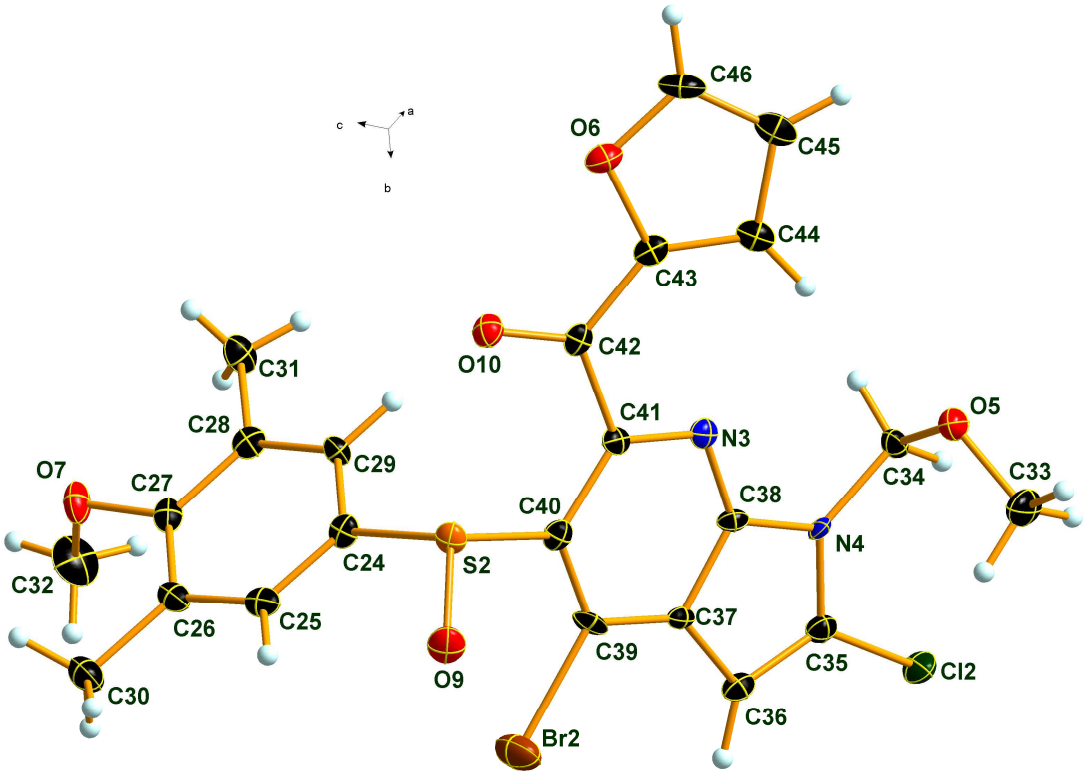


Figure 7: DIAMOND view of the molecular structure of compound **23a** (molecule B) in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 18: Molecular structure of compound **23a** (molecule B) in the crystal; selected atom distances (in Å).

Br2 – C39	1.886(4)	C24 – C29	1.399(5)
Cl2 – C35	1.715(4)	C25 – C26	1.391(7)
S2 – C24	1.815(3)	C26 – C27	1.411(5)
S2 – O9	1.497(3)	C26 – C30	1.508(6)
S2 – C40	1.839(4)	C27 – C28	1.402(5)
O5 – C33	1.424(6)	C28 – C29	1.395(5)
O5 – C34	1.412(5)	C28 – C31	1.514(5)
O6 – C43	1.380(5)	C35 – C36	1.369(5)

O6 – C46	1.360(5)	C36 – C37	1.432(5)
O7 – C32	1.435(6)	C37 – C38	1.420(5)
O7 – C27	1.388(4)	C37 – C39	1.400(5)
O10 – C42	1.228(4)	C39 – C40	1.389(5)
N3 – C38	1.326(5)	C40 – C41	1.429(5)
N3 – C41	1.335(5)	C41 – C42	1.503(5)
N4 – C34	1.464(5)	C42 – C43	1.477(5)
N4 – C35	1.380(6)	C43 – C44	1.356(5)
N4 – C38	1.379(5)	C44 – C45	1.420(7)
C24 – C25	1.392(5)	C45 – C46	1.346(7)

Table 19: Molecular structure of compound **23a** (molecule B) in the crystal; selected bond angles (in °).

C24 – S2 – C40	96.8(2)	N4 – C35 – C36	112.0(4)
O9 – S2 – C40	108.2(2)	C35 – C36 – C37	105.5(3)
O9 – S2 – C24	106.0(2)	C36 – C37 – C38	107.2(3)
C33 – O5 – C34	112.2(3)	C36 – C37 – C39	137.1(3)
C43 – O6 – C46	105.7(3)	C38 – C37 – C39	115.7(3)
C27 – O7 – C32	114.4(3)	N3 – C38 – N4	124.3(3)
C38 – N3 – C41	115.3(3)	N3 – C38 – C37	127.3(3)
C35 – N4 – C38	107.0(3)	N4 – C38 – C37	108.3(3)
C34 – N4 – C38	122.8(3)	Br2 – C39 – C37	115.7(3)
C34 – N4 – C35	130.1(3)	Br2 – C39 – C40	125.0(3)
S2 – C24 – C25	117.4(3)	C37 – C39 – C40	119.3(3)
S2 – C24 – C29	121.6(3)	S2 – C40 – C39	122.6(3)
C25 – C24 – C29	120.6(3)	S2 – C40 – C41	118.4(3)
C24 – C25 – C26	121.0(3)	C39 – C40 – C41	118.6(3)
C25 – C26 – C27	117.7(3)	N3 – C41 – C40	123.7(3)
C25 – C26 – C30	120.5(4)	N3 – C41 – C42	114.9(3)
C27 – C26 – C30	121.7(4)	C40 – C41 – C42	121.2(3)
O7 – C27 – C26	119.3(3)	O10 – C42 – C41	120.8(3)
O7 – C27 – C28	118.5(3)	O10 – C42 – C43	120.5(3)
C26 – C27 – C28	122.2(3)	C41 – C42 – C43	118.7(3)
C27 – C28 – C29	118.6(3)	O6 – C43 – C42	113.6(3)

C27 – C28 – C31	121.1(3)	O6 – C43 – C44	110.0(4)
C29 – C28 – C31	120.3(3)	C42 – C43 – C44	136.3(4)
C24 – C29 – C28	119.9(3)	C43 – C44 – C45	106.7(4)
O5 – C34 – N4	112.3(3)	C44 – C45 – C46	106.2(4)
Cl2 – C35 – N4	119.8(3)	O6 – C46 – C45	111.5(4)
Cl2 – C35 – C36	128.2(3)		

Table 20: Molecular structure of compound **23a** (molecule B) in the crystal; selected torsion angles (in °).

C24 – S2 – C40 – C41	105.0(3)	O7 – C27 – C28 – C29	175.2(4)
O9 – S2 – C40 – C41	-145.7(3)	O7 – C27 – C28 – C31	-2.0(5)
C40 – S2 – C24 – C29	-55.2(3)	C26 – C27 – C28 – C29	-1.7(5)
C24 – S2 – C40 – C39	-81.3(3)	C26 – C27 – C28 – C31	-178.9(4)
O9 – S2 – C24 – C25	20.3(3)	C31 – C28 – C29 – C24	178.5(4)
C40 – S2 – C24 – C25	131.5(3)	C27 – C28 – C29 – C24	1.3(6)
O9 – S2 – C24 – C29	-166.4(3)	Cl2 – C35 – C36 – C37	179.7(3)
O9 – S2 – C40 – C39	28.0(3)	N4 – C35 – C36 – C37	-0.6(4)
C33 – O5 – C34 – N4	68.6(4)	C35 – C36 – C37 – C39	179.8(4)
C43 – O6 – C46 – C45	0.6(5)	C35 – C36 – C37 – C38	0.8(4)
C46 – O6 – C43 – C44	-1.4(4)	C36 – C37 – C38 – N4	-0.7(4)
C46 – O6 – C43 – C42	177.3(3)	C39 – C37 – C38 – N3	-2.0(5)
C32 – O7 – C27 – C26	-88.6(4)	C39 – C37 – C38 – N4	180.0(3)
C32 – O7 – C27 – C28	94.5(4)	C36 – C37 – C39 – Br2	-1.1(6)
C38 – N3 – C41 – C42	-174.6(3)	C36 – C37 – C38 – N3	177.3(3)
C41 – N3 – C38 – N4	178.8(3)	C36 – C37 – C39 – C40	-178.9(4)
C41 – N3 – C38 – C37	1.1(5)	C38 – C37 – C39 – Br2	177.9(2)
C38 – N3 – C41 – C40	1.7(5)	C38 – C37 – C39 – C40	0.1(5)
C38 – N4 – C34 – O5	69.1(4)	Br2 – C39 – C40 – C41	-175.3(3)
C35 – N4 – C34 – O5	-106.8(4)	C37 – C39 – C40 – S2	-171.4(3)
C34 – N4 – C38 – C37	-176.3(3)	C37 – C39 – C40 – C41	2.3(5)
C35 – N4 – C38 – N3	-177.7(3)	Br2 – C39 – C40 – S2	11.0(4)
C38 – N4 – C35 – C36	0.1(4)	S2 – C40 – C41 – N3	170.6(3)
C38 – N4 – C35 – Cl2	179.9(3)	S2 – C40 – C41 – C42	-13.3(4)
C34 – N4 – C35 – C36	176.5(3)	C39 – C40 – C41 – N3	-3.4(5)

C35 – N4 – C38 – C37	0.4(4)	C39 – C40 – C41 – C42	172.7(3)
C34 – N4 – C38 – N3	5.6(5)	N3 – C41 – C42 – O10	162.9(3)
C34 – N4 – C35 – Cl2	-3.7(5)	N3 – C41 – C42 – C43	-16.4(5)
S2 – C24 – C25 – C26	175.2(3)	C40 – C41 – C42 – O10	-13.5(5)
C25 – C24 – C29 – C28	-1.4(6)	C40 – C41 – C42 – C43	167.2(3)
C29 – C24 – C25 – C26	1.8(6)	O10 – C42 – C43 – O6	-9.7(5)
S2 – C24 – C29 – C28	-174.4(3)	O10 – C42 – C43 – C44	168.5(4)
C24 – C25 – C26 – C27	-2.2(5)	C41 – C42 – C43 – O6	169.6(3)
C24 – C25 – C26 – C30	-179.5(4)	C41 – C42 – C43 – C44	-12.2(6)
C25 – C26 – C27 – C28	2.2(5)	O6 – C43 – C44 – C45	1.7(4)
C30 – C26 – C27 – O7	2.6(5)	C42 – C43 – C44 – C45	-176.6(4)
C30 – C26 – C27 – C28	179.5(4)	C43 – C44 – C45 – C46	-1.3(5)
C25 – C26 – C27 – O7	-174.7(3)	C44 – C45 – C46 – O6	0.4(5)

Compound 23b

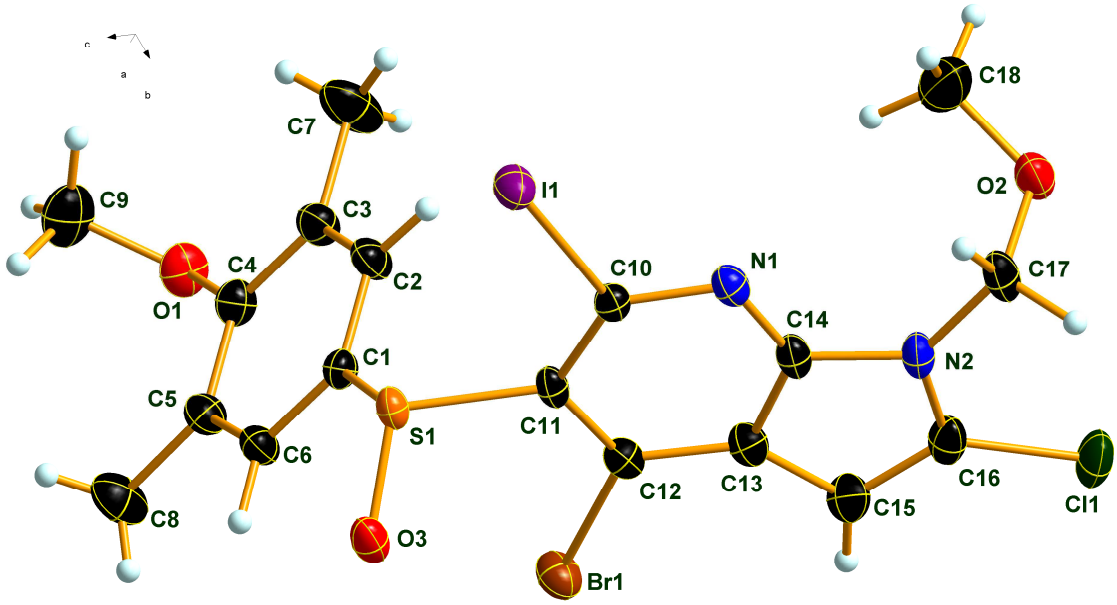


Figure 8: DIAMOND view of the molecular structure of compound **23b** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 21: Molecular structure of compound **23b** in the crystal; selected atom distances (in Å).

I1 – C10	2.111(3)	C1 – C2	1.398(5)
Br1 – C12	1.890(3)	C1 – C6	1.377(4)
Cl1 – C16	1.711(3)	C2 – C3	1.391(4)
S1 – O3	1.491(2)	C3 – C4	1.393(4)
S1 – C1	1.801(3)	C3 – C7	1.515(5)
S1 – C11	1.805(2)	C4 – C5	1.403(5)
O1 – C4	1.393(4)	C5 – C6	1.394(4)
O1 – C9	1.430(5)	C5 – C8	1.498(4)
O2 – C17	1.399(4)	C10 – C11	1.418(4)
O2 – C18	1.421(5)	C11 – C12	1.399(4)
N1 – C10	1.329(4)	C12 – C13	1.392(5)
N1 – C14	1.327(4)	C13 – C14	1.417(4)
N2 – C14	1.386(4)	C13 – C15	1.428(4)
N2 – C16	1.383(4)	C15 – C16	1.360(4)
N2 – C17	1.461(4)		

Table 22: Molecular structure of compound **23b** in the crystal; selected bond angles (in °).

O3 – S1 – C1	106.7(1)	C1 – C6 – C5	120.7(3)
O3 – S1 – C11	107.9(1)	I1 – C10 – N1	113.8(2)
C1 – S1 – C11	100.2(1)	I1 – C10 – C11	120.9(2)
C4 – O1 – C9	113.8(2)	N1 – C10 – C11	125.3(3)
C17 – O2 – C18	113.0(3)	S1 – C11 – C10	118.6(2)
C10 – N1 – C14	114.7(2)	S1 – C11 – C12	123.7(2)
C14 – N2 – C16	106.7(2)	C10 – C11 – C12	117.4(2)
C14 – N2 – C17	126.5(3)	Br1 – C12 – C11	122.9(2)
C16 – N2 – C17	126.8(3)	Br1 – C12 – C13	117.5(2)
S1 – C1 – C2	120.9(2)	C11 – C12 – C13	119.6(3)
S1 – C1 – C6	117.6(2)	C12 – C13 – C14	116.0(3)
C2 – C1 – C6	121.3(3)	C12 – C13 – C15	136.3(3)
C1 – C2 – C3	119.7(3)	C14 – C13 – C15	107.8(3)
C2 – C3 – C4	118.1(3)	N1 – C14 – N2	125.1(3)
C2 – C3 – C7	121.1(3)	N1 – C14 – C13	127.1(3)
C4 – C3 – C7	120.8(3)	N2 – C14 – C13	107.9(3)
O1 – C4 – C3	118.5(3)	C13 – C15 – C16	105.4(3)
O1 – C4 – C5	118.5(3)	Cl1 – C16 – N2	119.2(2)
C3 – C4 – C5	123.0(3)	Cl1 – C16 – C15	128.4(2)
C4 – C5 – C6	117.3(3)	N2 – C16 – C15	112.3(3)
C4 – C5 – C8	121.9(3)	O2 – C17 – N2	112.5(2)
C6 – C5 – C8	120.8(3)		

Table 23: Molecular structure of compound **23b** in the crystal; selected torsion angles (in °).

O3 – S1 – C1 – C2	-166.5(3)	C2 – C3 – C4 – O1	-178.8(3)
O3 – S1 – C1 – C6	20.3(3)	C2 – C3 – C4 – C5	-0.4(5)
C11 – S1 – C1 – C2	-54.1(3)	C7 – C3 – C4 – C5	177.8(3)
C11 – S1 – C1 – C6	132.6(3)	C7 – C3 – C4 – O1	-0.6(5)
O3 – S1 – C11 – C10	-128.2(2)	O1 – C4 – C5 – C6	179.4(3)
O3 – S1 – C11 – C12	45.1(3)	C3 – C4 – C5 – C6	1.0(5)
C1 – S1 – C11 – C10	120.5(3)	C3 – C4 – C5 – C8	-178.1(3)
C1 – S1 – C11 – C12	-66.3(3)	O1 – C4 – C5 – C8	0.3(5)

C9 – O1 – C4 – C3	-96.7(3)	C4 – C5 – C6 – C1	-0.6(5)
C9 – O1 – C4 – C5	84.9(4)	C8 – C5 – C6 – C1	178.5(3)
C18 – O2 – C17 – N2	78.3(3)	I1 – C10 – C11 – S1	-7.9(3)
C10 – N1 – C14 – C13	0.2(4)	N1 – C10 – C11 – S1	173.1(2)
C14 – N1 – C10 – I1	-179.1(2)	I1 – C10 – C11 – C12	178.5(2)
C14 – N1 – C10 – C11	0.0(4)	N1 – C10 – C11 – C12	-0.5(5)
C10 – N1 – C14 – N2	-180.0(3)	S1 – C11 – C12 – Br1	7.3(4)
C14 – N2 – C16 – C15	-1.1(4)	C10 – C11 – C12 – C13	0.9(4)
C14 – N2 – C17 – O2	-96.8(3)	S1 – C11 – C12 – C13	-172.5(2)
C16 – N2 – C17 – O2	80.8(4)	C10 – C11 – C12 – Br1	-179.4(2)
C16 – N2 – C14 – N1	-179.1(3)	C11 – C12 – C13 – C14	-0.7(4)
C17 – N2 – C14 – N1	-1.1(5)	Br1 – C12 – C13 – C14	179.6(2)
C16 – N2 – C14 – C13	0.8(3)	Br1 – C12 – C13 – C15	0.2(5)
C17 – N2 – C14 – C13	178.8(3)	C11 – C12 – C13 – C15	180.0(3)
C17 – N2 – C16 – Cl1	-0.5(4)	C12 – C13 – C15 – C16	179.0(4)
C14 – N2 – C16 – Cl1	177.5(2)	C12 – C13 – C14 – N2	-179.7(3)
C17 – N2 – C16 – C15	-179.1(3)	C14 – C13 – C15 – C16	-0.5(4)
C2 – C1 – C6 – C5	-0.4(5)	C12 – C13 – C14 – N1	0.1(5)
S1 – C1 – C2 – C3	-172.0(2)	C15 – C13 – C14 – N1	179.7(3)
C6 – C1 – C2 – C3	1.0(5)	C15 – C13 – C14 – N2	-0.2(4)
S1 – C1 – C6 – C5	172.9(2)	C13 – C15 – C16 – N2	1.0(4)
C1 – C2 – C3 – C4	-0.6(5)	C13 – C15 – C16 – Cl1	-177.5(3)
C1 – C2 – C3 – C7	-178.8(3)		

Compound 27a

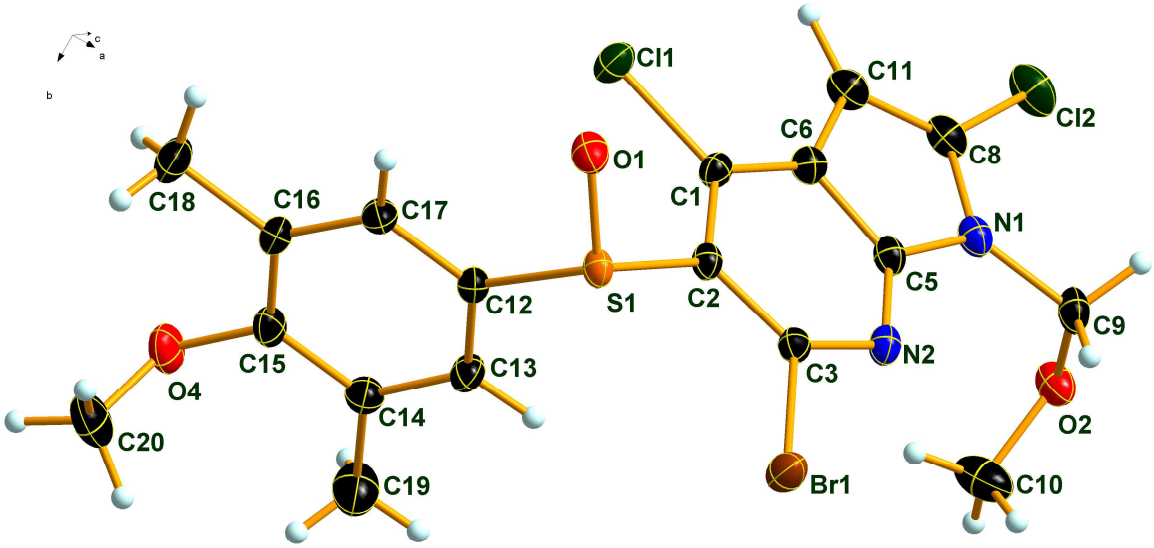


Figure 9: DIAMOND view of the molecular structure of compound **27a** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 24: Molecular structure of compound **27a** in the crystal; selected atom distances (in Å).

Br1 – C3	1.898(2)	C1 – C2	1.398(3)
Cl1 – C1	1.727(2)	C1 – C6	1.388(3)
Cl2 – C8	1.705(2)	C2 – C3	1.413(3)
S1 – O1	1.490(2)	C5 – C6	1.418(3)
S1 – C2	1.805(2)	C6 – C11	1.434(3)
S1 – C12	1.804(2)	C8 – C11	1.357(3)
O2 – C9	1.398(3)	C12 – C13	1.389(3)
O2 – C10	1.428(3)	C12 – C17	1.386(3)
O4 – C15	1.390(3)	C13 – C14	1.393(3)
O4 – C20	1.432(4)	C14 – C15	1.403(3)
N1 – C5	1.382(3)	C14 – C19	1.505(3)
N1 – C8	1.387(3)	C15 – C16	1.395(3)
N1 – C9	1.464(3)	C16 – C17	1.394(3)
N2 – C3	1.321(3)	C16 – C18	1.512(3)
N2 – C5	1.332(3)		

Table 25: Molecular structure of compound **27a** in the crystal; selected bond angles (in °).

O1 – S1 – C2	107.8(1)	C1 – C6 – C11	136.3(2)
O1 – S1 – C12	107.2(1)	C5 – C6 – C11	107.7(2)
C2 – S1 – C12	99.3(1)	Cl2 – C8 – N1	119.3(2)
C9 – O2 – C10	113.3(2)	Cl2 – C8 – C11	128.7(2)
C15 – O4 – C20	112.8(2)	N1 – C8 – C11	112.1(2)
C5 – N1 – C8	107.1(2)	O2 – C9 – N1	112.4(2)
C5 – N1 – C9	126.4(2)	C6 – C11 – C8	105.5(2)
C8 – N1 – C9	126.5(2)	S1 – C12 – C13	120.8(2)
C3 – N2 – C5	114.1(2)	S1 – C12 – C17	117.1(2)
Cl1 – C1 – C2	122.3(2)	C13 – C12 – C17	121.6(2)
Cl1 – C1 – C6	118.4(2)	C12 – C13 – C14	119.9(2)
C2 – C1 – C6	119.4(2)	C13 – C14 – C15	117.8(2)
S1 – C2 – C1	122.8(2)	C13 – C14 – C19	121.1(2)
S1 – C2 – C3	119.6(2)	C15 – C14 – C19	121.1(2)
C1 – C2 – C3	117.3(2)	O4 – C15 – C14	118.2(2)
Br1 – C3 – N2	114.3(1)	O4 – C15 – C16	119.1(2)
Br1 – C3 – C2	119.6(2)	C14 – C15 – C16	122.7(2)
N2 – C3 – C2	126.0(2)	C15 – C16 – C17	118.1(2)
N1 – C5 – N2	125.1(2)	C15 – C16 – C18	121.0(2)
N1 – C5 – C6	107.8(2)	C17 – C16 – C18	120.9(2)
N2 – C5 – C6	127.1(2)	C12 – C17 – C16	119.8(2)
C1 – C6 – C5	116.0(2)		

Table 26: Molecular structure of compound **27a** in the crystal; selected torsion angles (in °).

O1 – S1 – C2 – C1	-44.3(2)	C2 – C1 – C6 – C5	0.0(3)
O1 – S1 – C2 – C3	129.2(2)	C2 – C1 – C6 – C11	179.6(2)
C12 – S1 – C2 – C1	67.2(2)	S1 – C2 – C3 – Br1	7.3(2)
C12 – S1 – C2 – C3	-119.3(2)	S1 – C2 – C3 – N2	-173.6(2)
O1 – S1 – C12 – C13	166.7(2)	C1 – C2 – C3 – Br1	-178.9(2)
O1 – S1 – C12 – C17	-21.3(2)	C1 – C2 – C3 – N2	0.3(3)
C2 – S1 – C12 – C13	54.6(2)	N1 – C5 – C6 – C1	-180.0(2)
C2 – S1 – C12 – C17	-133.3(2)	N1 – C5 – C6 – C11	0.3(2)

C10 – O2 – C9 – N1	-77.1(3)	N2 – C5 – C6 – C1	0.6(3)
C20 – O4 – C15 – C14	96.2(2)	N2 – C5 – C6 – C11	-179.1(2)
C20 – O4 – C15 – C16	-85.8(3)	C1 – C6 – C11 – C8	-179.3(2)
C8 – N1 – C5 – N2	178.6(2)	C5 – C6 – C11 – C8	0.4(2)
C8 – N1 – C5 – C6	-0.8(2)	Cl2 – C8 – C11 – C6	177.5(2)
C9 – N1 – C5 – N2	1.7(3)	N1 – C8 – C11 – C6	-0.9(2)
C9 – N1 – C5 – C6	-177.7(2)	S1 – C12 – C13 – C14	170.2(2)
C5 – N1 – C8 – Cl2	-177.5(2)	C17 – C12 – C13 – C14	-1.5(3)
C5 – N1 – C8 – C11	1.1(2)	S1 – C12 – C17 – C16	-171.3(2)
C9 – N1 – C8 – Cl2	-0.6(3)	C13 – C12 – C17 – C16	0.6(3)
C9 – N1 – C8 – C11	178.0(2)	C12 – C13 – C14 – C15	0.1(3)
C5 – N1 – C9 – O2	96.5(2)	C12 – C13 – C14 – C19	179.6(2)
C8 – N1 – C9 – O2	-79.8(3)	C13 – C14 – C15 – O4	-179.8(2)
C5 – N2 – C3 – Br1	179.4(2)	C13 – C14 – C15 – C16	2.2(3)
C5 – N2 – C3 – C2	0.2(3)	C19 – C14 – C15 – O4	0.6(3)
C3 – N2 – C5 – N1	180.0(2)	C19 – C14 – C15 – C16	-177.3(2)
C3 – N2 – C5 – C6	-0.7(3)	O4 – C15 – C16 – C17	179.0(2)
Cl1 – C1 – C2 – S1	-7.0(3)	O4 – C15 – C16 – C18	-0.9(3)
Cl1 – C1 – C2 – C3	179.3(2)	C14 – C15 – C16 – C17	-3.1(3)
C6 – C1 – C2 – S1	173.3(2)	C14 – C15 – C16 – C18	177.1(2)
C6 – C1 – C2 – C3	-0.4(3)	C15 – C16 – C17 – C12	1.6(3)
Cl1 – C1 – C6 – C5	-179.8(2)	C18 – C16 – C17 – C12	-178.5(2)
Cl1 – C1 – C6 – C11	-0.1(3)		

Compound 27b

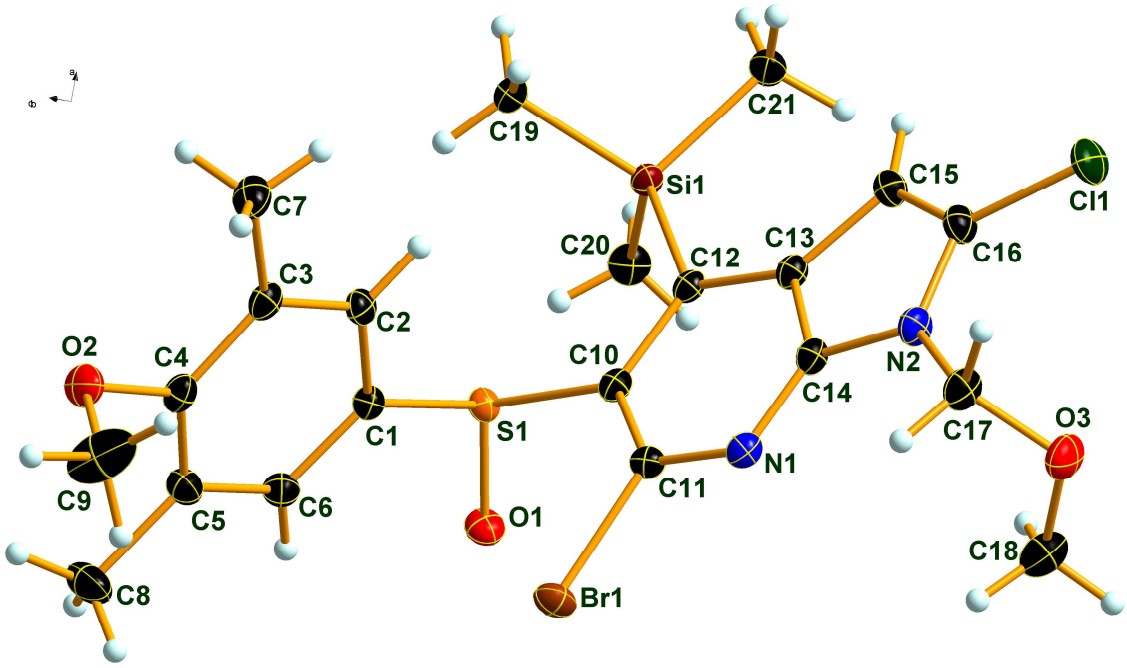


Figure 10: DIAMOND view of the molecular structure of compound **27b** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 27: Molecular structure of compound **27b** in the crystal; selected atom distances (in Å).

Br1 – C11	1.899(2)	N2 – C16	1.384(2)
Cl1 – C16	1.711(2)	N2 – C17	1.458(2)
S1 – O1	1.490(1)	C1 – C2	1.397(2)
S1 – C1	1.792(2)	C1 – C6	1.383(2)
S1 – C10	1.798(2)	C2 – C3	1.392(2)
Si1 – C12	1.927(2)	C3 – C4	1.400(2)
Si1 – C19	1.868(2)	C3 – C7	1.505(2)
Si1 – C20	1.872(2)	C4 – C5	1.395(2)
Si1 – C21	1.863(2)	C5 – C6	1.396(2)
O2 – C4	1.389(2)	C5 – C8	1.511(2)
O2 – C9	1.423(3)	C10 – C11	1.408(2)
O3 – C17	1.396(2)	C10 – C12	1.417(2)
O3 – C18	1.428(2)	C12 – C13	1.410(2)
N1 – C11	1.322(2)	C13 – C14	1.419(2)
N1 – C14	1.333(2)	C13 – C15	1.443(2)
N2 – C14	1.376(2)	C15 – C16	1.353(2)

Table 28: Molecular structure of compound **27b** in the crystal; selected bond angles (in °).

O1 – S1 – C1	107.7(1)	C4 – C5 – C6	117.9(2)
O1 – S1 – C10	110.0(1)	C4 – C5 – C8	122.0(2)
C1 – S1 – C10	100.9(1)	C6 – C5 – C8	120.1(2)
C12 – Si1 – C19	107.5(1)	C1 – C6 – C5	120.1(2)
C12 – Si1 – C20	110.8(1)	S1 – C10 – C11	123.7(1)
C12 – Si1 – C21	111.2(1)	S1 – C10 – C12	115.1(1)
C19 – Si1 – C20	114.5(1)	C11 – C10 – C12	121.1(1)
C19 – Si1 – C21	107.1(1)	Br1 – C11 – N1	113.6(1)
C20 – Si1 – C21	105.7(1)	Br1 – C11 – C10	121.6(1)
C4 – O2 – C9	112.4(1)	N1 – C11 – C10	124.8(1)
C17 – O3 – C18	113.6(1)	Si1 – C12 – C10	121.9(1)
C11 – N1 – C14	114.0(1)	Si1 – C12 – C13	123.5(1)
C14 – N2 – C16	106.4(1)	C10 – C12 – C13	114.6(1)
C14 – N2 – C17	125.5(1)	C12 – C13 – C14	118.0(1)
C16 – N2 – C17	128.1(1)	C12 – C13 – C15	136.3(2)
S1 – C1 – C2	120.1(1)	C14 – C13 – C15	105.7(1)
S1 – C1 – C6	118.1(1)	N1 – C14 – N2	123.1(1)
C2 – C1 – C6	121.5(2)	N1 – C14 – C13	127.5(2)
C1 – C2 – C3	119.5(1)	N2 – C14 – C13	109.5(1)
C2 – C3 – C4	118.2(2)	C13 – C15 – C16	106.4(1)
C2 – C3 – C7	121.1(2)	Cl1 – C16 – N2	119.4(1)
C4 – C3 – C7	120.6(1)	Cl1 – C16 – C15	128.6(1)
O2 – C4 – C3	117.7(1)	N2 – C16 – C15	112.1(1)
O2 – C4 – C5	119.5(1)	O3 – C17 – N2	113.6(1)
C3 – C4 – C5	122.7(2)		

Table 29: Molecular structure of compound **27b** in the crystal; selected torsion angles (in °).

O1 – S1 – C1 – C2	169.1(1)	C2 – C1 – C6 – C5	-2.9(2)
O1 – S1 – C1 – C6	-18.2(2)	C1 – C2 – C3 – C4	0.2(2)
C10 – S1 – C1 – C2	53.8(1)	C1 – C2 – C3 – C7	-178.1(2)
C10 – S1 – C1 – C6	-133.5(1)	C2 – C3 – C4 – O2	-179.1(1)
O1 – S1 – C10 – C11	-55.4(2)	C2 – C3 – C4 – C5	-2.5(2)
O1 – S1 – C10 – C12	122.2(1)	C7 – C3 – C4 – O2	-0.8(2)
C1 – S1 – C10 – C11	58.1(2)	C7 – C3 – C4 – C5	175.8(2)

C1 – S1 – C10 – C12	-124.3(1)	O2 – C4 – C5 – C6	178.6(2)
C19 – Si1 – C12 – C10	67.8(1)	O2 – C4 – C5 – C8	-1.0(2)
C19 – Si1 – C12 – C13	-110.5(1)	C3 – C4 – C5 – C6	2.1(2)
C20 – Si1 – C12 – C10	-58.0(1)	C3 – C4 – C5 – C8	-177.5(2)
C20 – Si1 – C12 – C13	123.8(1)	C4 – C5 – C6 – C1	0.6(2)
C21 – Si1 – C12 – C10	-175.3(1)	C8 – C5 – C6 – C1	-179.8(2)
C21 – Si1 – C12 – C13	6.5(2)	S1 – C10 – C11 – Br1	1.2(2)
C9 – O2 – C4 – C3	-98.2(2)	S1 – C10 – C11 – N1	179.5(1)
C9 – O2 – C4 – C5	85.1(2)	C12 – C10 – C11 – Br1	-176.3(1)
C18 – O3 – C17 – N2	-64.4(2)	C12 – C10 – C11 – N1	2.0(3)
C14 – N1 – C11 – Br1	177.9(1)	S1 – C10 – C12 – Si1	1.9(2)
C14 – N1 – C11 – C10	-0.5(2)	S1 – C10 – C12 – C13	-179.7(1)
C11 – N1 – C14 – N2	178.8(2)	C11 – C10 – C12 – Si1	179.6(1)
C11 – N1 – C14 – C13	-0.7(2)	C11 – C10 – C12 – C13	-2.0(2)
C16 – N2 – C14 – N1	-179.9(2)	Si1 – C12 – C13 – C14	179.2(1)
C16 – N2 – C14 – C13	-0.3(2)	Si1 – C12 – C13 – C15	0.1(3)
C17 – N2 – C14 – N1	-2.1(3)	C10 – C12 – C13 – C14	0.8(2)
C17 – N2 – C14 – C13	177.6(2)	C10 – C12 – C13 – C15	-178.2(2)
C14 – N2 – C16 – Cl1	180.0(1)	C12 – C13 – C14 – N1	0.6(3)
C14 – N2 – C16 – C15	0.1(2)	C12 – C13 – C14 – N2	-179.0(1)
C17 – N2 – C16 – Cl1	2.3(2)	C15 – C13 – C14 – N1	179.9(2)
C17 – N2 – C16 – C15	-177.6(2)	C15 – C13 – C14 – N2	0.3(2)
C14 – N2 – C17 – O3	107.3(2)	C12 – C13 – C15 – C16	179.0(2)
C16 – N2 – C17 – O3	-75.3(2)	C14 – C13 – C15 – C16	-0.2(2)
S1 – C1 – C2 – C3	174.9(1)	C13 – C15 – C16 – Cl1	-179.8(1)
C6 – C1 – C2 – C3	2.4(2)	C13 – C15 – C16 – N2	0.0(2)
S1 – C1 – C6 – C5	-175.5(1)		

Compound 37

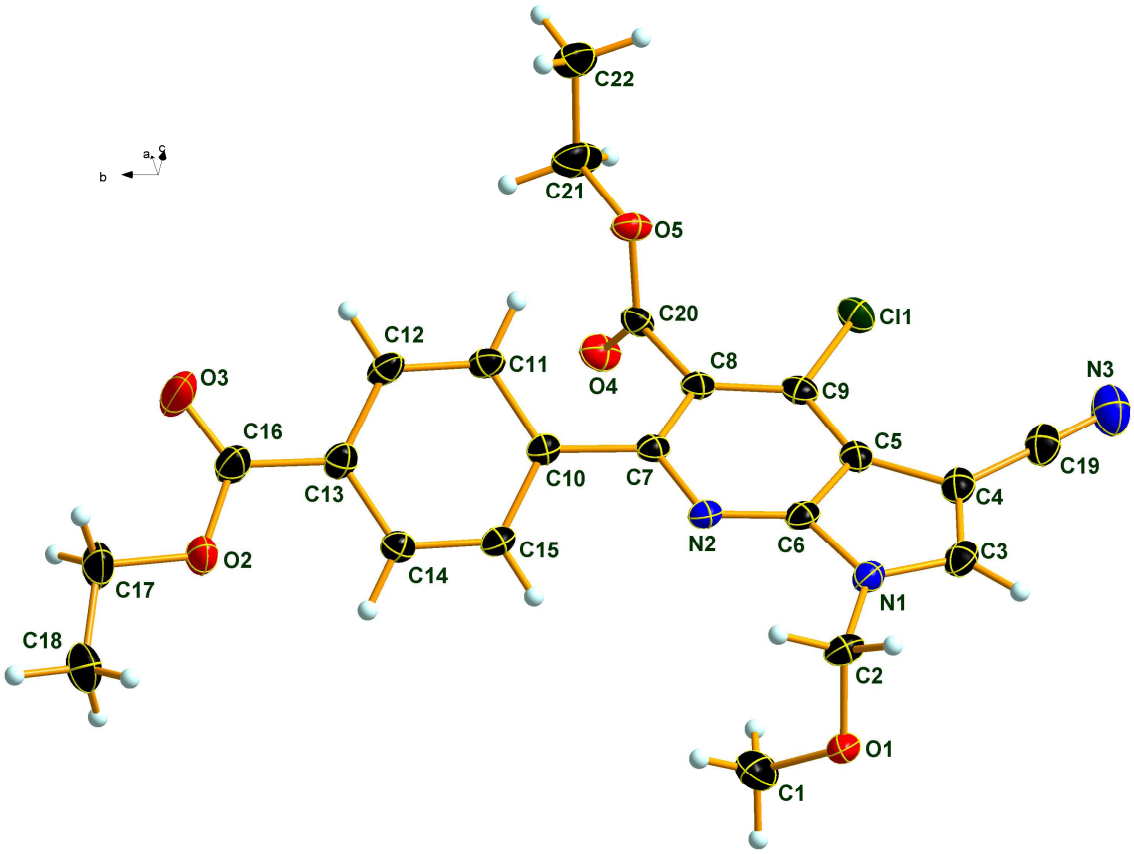


Figure 11: DIAMOND view of the molecular structure of compound **37** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 30: Molecular structure of compound **37** in the crystal; selected atom distances (in Å).

Cl1 – C9	1.726(2)	C4 – C19	1.430(3)
O1 – C1	1.422(3)	C5 – C6	1.406(3)
O1 – C2	1.399(2)	C5 – C9	1.393(3)
O2 – C16	1.336(2)	C7 – C8	1.421(3)
O2 – C17	1.453(2)	C7 – C10	1.490(2)
O3 – C16	1.205(3)	C8 – C9	1.387(3)
O4 – C20	1.206(2)	C8 – C20	1.504(3)
O5 – C20	1.333(2)	C10 – C11	1.397(2)
O5 – C21	1.460(3)	C10 – C15	1.395(2)
N1 – C2	1.459(2)	C11 – C12	1.384(3)
N1 – C3	1.362(2)	C12 – C13	1.396(3)
N1 – C6	1.383(2)	C13 – C14	1.394(3)
N2 – C6	1.329(2)	C13 – C16	1.490(3)
N2 – C7	1.344(2)	C14 – C15	1.376(3)

N3 – C19	1.146(3)	C17 – C18	1.492(3)
C3 – C4	1.378(3)	C21 – C22	1.493(3)
C4 – C5	1.436(3)		

Table 31: Molecular structure of compound **37** in the crystal; selected bond angles (in °).

C1 – O1 – C2	113.0(2)	C9 – C8 – C20	118.2(2)
C16 – O2 – C17	116.6(2)	Cl1 – C9 – C5	120.2(1)
C20 – O5 – C21	115.6(1)	Cl1 – C9 – C8	120.5(1)
C2 – N1 – C3	125.3(2)	C5 – C9 – C8	119.3(2)
C2 – N1 – C6	126.3(2)	C7 – C10 – C11	123.1(2)
C3 – N1 – C6	108.4(2)	C7 – C10 – C15	118.0(2)
C6 – N2 – C7	115.5(2)	C11 – C10 – C15	118.9(2)
O1 – C2 – N1	112.8(2)	C10 – C11 – C12	120.3(2)
N1 – C3 – C4	110.5(2)	C11 – C12 – C13	120.4(2)
C3 – C4 – C5	106.3(2)	C12 – C13 – C14	119.1(2)
C3 – C4 – C19	125.2(2)	C12 – C13 – C16	119.2(2)
C5 – C4 – C19	128.4(2)	C14 – C13 – C16	121.7(2)
C4 – C5 – C6	106.8(2)	C13 – C14 – C15	120.4(2)
C4 – C5 – C9	137.8(2)	C10 – C15 – C14	120.8(2)
C6 – C5 – C9	115.5(2)	O2 – C16 – O3	122.7(2)
N1 – C6 – N2	124.1(2)	O2 – C16 – C13	112.9(2)
N1 – C6 – C5	108.1(2)	O3 – C16 – C13	124.4(2)
N2 – C6 – C5	127.8(2)	O2 – C17 – C18	107.4(2)
N2 – C7 – C8	122.5(2)	N3 – C19 – C4	178.5(2)
N2 – C7 – C10	114.8(2)	O4 – C20 – O5	124.5(2)
C8 – C7 – C10	122.7(2)	O4 – C20 – C8	123.0(2)
C7 – C8 – C9	119.5(2)	O5 – C20 – C8	112.5(1)
C7 – C8 – C20	121.8(2)	O5 – C21 – C22	108.0(2)

Table 32: Molecular structure of compound **37** in the crystal; selected torsion angles (in °).

C1 – O1 – C2 – N1	-76.9(2)	C6 – C5 – C9 – C8	0.3(2)
C17 – O2 – C16 – O3	-1.7(3)	N2 – C7 – C8 – C9	-0.4(2)
C17 – O2 – C16 – C13	178.0(2)	N2 – C7 – C8 – C20	172.2(1)
C16 – O2 – C17 – C18	-170.7(2)	C10 – C7 – C8 – C9	-178.4(2)
C21 – O5 – C20 – O4	-1.0(3)	C10 – C7 – C8 – C20	-5.8(2)

C21 – O5 – C20 – C8	177.9(2)	N2 – C7 – C10 – C11	139.0(2)
C20 – O5 – C21 – C22	178.4(2)	N2 – C7 – C10 – C15	-38.6(2)
C3 – N1 – C2 – O1	-76.6(2)	C8 – C7 – C10 – C11	-42.9(2)
C6 – N1 – C2 – O1	102.9(2)	C8 – C7 – C10 – C15	139.5(2)
C2 – N1 – C3 – C4	179.6(2)	C7 – C8 – C9 – Cl1	179.2(1)
C6 – N1 – C3 – C4	-0.1(2)	C7 – C8 – C9 – C5	0.0(2)
C2 – N1 – C6 – N2	0.3(3)	C20 – C8 – C9 – Cl1	6.4(2)
C2 – N1 – C6 – C5	-179.7(2)	C20 – C8 – C9 – C5	-172.9(2)
C3 – N1 – C6 – N2	179.9(2)	C7 – C8 – C20 – O4	-81.5(2)
C3 – N1 – C6 – C5	-0.1(2)	C7 – C8 – C20 – O5	99.6(2)
C7 – N2 – C6 – N1	179.8(2)	C9 – C8 – C20 – O4	91.2(2)
C7 – N2 – C6 – C5	-0.2(2)	C9 – C8 – C20 – O5	-87.8(2)
C6 – N2 – C7 – C8	0.5(2)	C7 – C10 – C11 – C12	-178.2(2)
C6 – N2 – C7 – C10	178.6(1)	C15 – C10 – C11 – C12	-0.6(3)
N1 – C3 – C4 – C5	0.2(2)	C7 – C10 – C15 – C14	178.0(2)
N1 – C3 – C4 – C19	176.6(2)	C11 – C10 – C15 – C14	0.3(3)
C3 – C4 – C5 – C6	-0.3(2)	C10 – C11 – C12 – C13	0.5(3)
C3 – C4 – C5 – C9	-179.7(2)	C11 – C12 – C13 – C14	-0.1(3)
C19 – C4 – C5 – C6	-176.6(2)	C11 – C12 – C13 – C16	178.3(2)
C19 – C4 – C5 – C9	4.0(3)	C12 – C13 – C14 – C15	-0.3(3)
C4 – C5 – C6 – N1	0.3(2)	C16 – C13 – C14 – C15	-178.6(2)
C4 – C5 – C6 – N2	-179.7(2)	C12 – C13 – C16 – O2	-172.3(2)
C9 – C5 – C6 – N1	179.8(1)	C12 – C13 – C16 – O3	7.4(3)
C9 – C5 – C6 – N2	-0.2(3)	C14 – C13 – C16 – O2	6.0(3)
C4 – C5 – C9 – Cl1	0.5(3)	C14 – C13 – C16 – O3	-174.3(2)
C4 – C5 – C9 – C8	179.7(2)	C13 – C14 – C15 – C10	0.1(3)
C6 – C5 – C9 – Cl1	-179.0(1)		

Single crystals of compounds **18**, **23a**, **23b**, **27a**, **27b** and **37**, suitable for X-ray diffraction, were obtained by slow evaporation of heptane- and EtOAc- as well as heptane/EtOAc-solutions at ambient temperature. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å). Data collection was

performed with the CrysAlis CCD software;[228] CrysAlis RED software[229] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[230] was applied. The structures were solved with SHELXS-97,[231] refined with SHELXL-97[232] and finally checked using PLATON.[233] Details for data collection and structure refinement are summarized in Table 33.

CCDC-935382 (for **18**), CCDC-935383 (for **23a**), CCDC-935384 (for **23b**), CCDC-935385 (for **27a**), CCDC-935386 (for **27b**) and CCDC-935387 (for **37**) contain supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[228] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.25p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[229] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[230] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.
[231] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[232] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[233] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 33: Details for X-ray data collection and structure refinement for compounds **18**, **23a**, **23b**, **27a**, **27b** and **37**.

	18	**23a**	**23b**	**27a**	**27b**	**37**
Empirical formula	$C1_8H_{18}BrClN_2O_3S$	$C_{23}H_{20}BrClN_2O_5S$	$C_{18}H_{17}BrClIN_2O_3S$	$C_{18}H_{17}BrCl_2N_2O_3S$	$C_{21}H_{26}BrClN_2O_3SSi$	$C_{22}H_{20}ClN_3O_5$
Formula mass	457.76	551.83	583.66	492.21	529.95	441.86
T [K]	173(2)	100(2)	173(2)	173(2)	100(2)	100(2)
Crystal size [mm]	0.40 × 0.05 × 0.02	0.323 × 0.165 × 0.060	0.20 × 0.20 × 0.05	0.35 × 0.50 × 0.10	0.291 × 0.217 × 0.124	0.394 × 0.130 × 0.093
Crystal description	colorless needle	yellow plate	colorless plate	colorless block	colorless block	colorless rod
Crystal system	orthorhombic	monoclinic	triclinic	triclinic	monoclinic	monoclinic
Space group	*P*212121	*P*21	*P*-1	*P*-1	*P*21/*c*	*C*2/*c*
a [Å]	4.9696(8)	11.9059(3)	9.5042(3)	9.3044(4)	8.2438(2)	13.7450(9)
b [Å]	13.2592(16)	11.7627(3)	10.1673(4)	9.9525(5)	14.4827(5)	21.0674(12)
c [Å]	28.498(5)	16.5808(4)	11.3146(5)	11.3242(5)	20.0180(6)	15.7003(10)
α [°]	90.0	90.0	109.730(4)	109.139(4)	90.0	90.0
β [°]	90.0	91.969(2)	91.576(3)	90.791(4)	92.678(3)	108.555(7)
γ [°]	90.0	90.0	90.006(3)	92.080(3)	90.0	90.0
V [$Å^3$]	1877.8(5)	2320.70(10)	1028.73(7)	989.66(8)	2387.39(12)	4310.0(5)
Z	4	4	2	2	4	8
$\rho_{calcd.}$ [g cm^{-3}]	1.619	1.579	1.884	1.652	1.474	1.362
μ [mm^{-1}]	2.463	2.015	3.751	2.474	1.996	0.216
F(000)	928	1120	568	496	1088	1840
Θ range [°]	4.16 – 28.28	4.15 – 28.28	4.23 – 26.37	4.31 – 28.28	4.16 – 30.03	4.26 – 28.28
Index ranges	$-6 \le h \le 6$	$-15 \le h \le 15$	$-11 \le h \le 11$	$-12 \le h \le 12$	$-11 \le h \le 11$	$-18 \le h \le 18$
	$-17 \le k \le 14$	$-15 \le k \le 15$	$-12 \le k \le 12$	$-13 \le k \le 13$	$-20 \le k \le 20$	$-25 \le k \le 28$
	$-36 \le l \le 37$	$-22 \le l \le 22$	$-14 \le l \le 14$	$-15 \le l \le 15$	$-28 \le l \le 28$	$-20 \le l \le 19$
Reflns. collected	11655	27987	9477	11218	47758	19582
Reflns. obsd.	3281	9347	3653	4292	5824	3681
Reflns. unique	4601	11435	4169	4871	6960	5319
	(R_{int} = 0.0820)	(R_{int} = 0.0573)	(R_{int} = 0.0230)	(R_{int} = 0.0265)	(R_{int} = 0.0436)	(R_{int} = 0.0550)
R_1, wR_2 (2σ data)	0.0574, 0.0738	0.0464, 0.0921	0.0259, 0.0607	0.0313, 0.0782	0.0295, 0.0650	0.0453, 0.0932
R_1, wR_2 (all data)	0.0971, 0.0845	0.0643, 0.1012	0.0324, 0.0641	0.0381, 0.0826	0.0417, 0.0704	0.0765, 0.1071
GOOF on F^2	1.009	1.018	1.044	1.042	1.055	1.018
Peak/hole [e $Å^{-3}$]	0.976 / -0.592	1.019 / -0.606	0.950 / -0.535	0.886 / -0.588	0.595 / -0.317	0.298 / -0.253